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A NEW MICROBODY FOUND IN THE BLOOD IN A CASE OF MYELOGENOUS LEUKEMIA AND THE EFFICACY OF ARSPHENAMIN ON THE DISEASE *

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In pathogenesis, chloroma is closely related to leukemia, so that although the former is regarded by some authors as belonging to the malignant tumor group, it is now generally accepted that chloroma is an atypical form of leukemia. It is well known that the exact clinical diagnosis of chloroma is sometimes extremely difficult. In our case it seems probably justifiable to consider the disease as myeloblast-chloroleukemia, but from the clinical point of view, without performing necropsy, we think it may be proper to call it an acute myeloblast-leukemia, with the accompaniment of a chloroma-like tumor in the skull.

REPORT OF CASE

History.—A boy aged 5 years and 9 months, with a negative family history, entered the hospital Dec. 13, 1915. Two years previously, he had had acute nephritis and in the previous May, whooping cough, followed by diphtheria and measles, successively. The onset of the present illness was ten days before admission. At the onset he developed a sudden rise of temperature, with swollen neck and a sore throat. The fever had been continuous to the time of admission. His appetite was poor, his bowels regular.

Physical Examination.—On admission the patient looked like one suffering from scarlet fever of a severe form. His face expressed great anxiety and the breathing was jerky, owing to the swelling of the throat. There was no delirium. The boy was of moderate size, and of slight frame. He was emaciated. The skin showed nothing worth mentioning, neither change in color, eruption, nor desquamation. The development of the subcutaneous fat was poor. The pulse was regular in rhythm, but increased in frequency (130 per minute). Its tension was moderate. His tongue was dry. There was strong *foetor ex ore*. Both tonsils were enlarged and intensely reddened. The pharyngeal mucous membrane was also involved in the congestion, but there was no sign of ulcer or pseudomembrane. The cervical glands on both sides were enlarged to bean size and were painful on pressure. They were hard and firm. No notable change in the viscera of thorax and abdomen could be found. The thymus was not enlarged. The edge of the liver was palpable

* Submitted for publication May 1, 1918.

* From the Department of Pediatrics, Japanese Medical School Hospital, Mukden, South Manchuria, China.

at the costal margin in the right mammary line. The spleen was not felt. Neither thickening nor aching in the bones were present. The urine was acid in reaction and slightly turbid. Albumin was absent, but the diazo reaction was strongly positive.

Course of the Malady.—The general course of the disease is summarized in the accompanying chart. Therefore, only some clinical findings particularly worthy of mention will be noted.

Dec. 17, 1915. Albumin occurred in the urine in small amount. The diazo reaction was strongly positive. On examination of the urinary deposits microscopically, some leukocytes alone were found. No further change in the pharynx was noted. The swollen glands of the neck increased in number and size. The pharyngeal mucus showed mostly the *Staphylococcus albus.*

December 21. Hematuria occurred. The angina was still severe. Markedly enlarged lymphatic glands of the size of a bean or that of a lentil were counted to the number of nine on each side of the neck. Many other smaller ones were felt also. The glands in the axilla, elbow and groin became involved in the swelling. Many of them were of lentil size.

December 23. Hematuria continued. In the evening the boy had a chill followed by the appearance of many petechia on the front of the left arm. The pharyngeal congestion was markedly diminished. Pallor increased. The upper limit of the liver was situated in the normal position. The lower edge, however, was easily felt 2 cm. below the costal margin in the mammary line. No remarkable change in the character of the edge was detected. The spleen was not palpable.

December 24. The first intramuscular injection of 0.15 gm. neo-arsphenamin was given.

December 26. The hematuria increased. The urinary sediment contained many blood corpuscles and a few casts. The boy's appetite continued poor. No sign of edema was found.

December 28. The congestion of the throat had almost entirely disappeared. The appetite was lost entirely. The liver diminished in size. It was no longer felt.

December 30. Besides blood cells, many hyaline and granular casts were found in the urinary deposits.

Jan. 4, 1916. A second injection of neo-arsphenamin in doses of 0.2 gm. was given intramuscularly.

January 6. Emaciation and paleness were remarkably increased. Hematuria still continued. The patient, however, remained still vigorous. His appetite got better. There was no sore throat. During the previous few days bone-ache in the right leg became pronounced.

January 11. The bone-ache disappeared. Glandular enlargement diminished markedly, so that only a few small glands could be felt. The boy was cheerful. The amount of blood in the urine decreased considerably. A tumor of a cherry size appeared on the frontal bone at the upper margin of the right orbital cavity, so that the eyelid was distended. It had no connection with the eyeball and was of a cartilaginous consistence, with a smooth surface. No pain, either spontaneous or on pressure, was felt.

January 18. The urine contained a trace of albumin, but showed nothing microscopically.

January 20. The urine was normal.

January 22. The orbital neoplasm became further enlarged. No pigmentation was observed either on or through the skin over the tumor. Sight and hearing were not affected. The third intramuscular injection of 0.1 gm. arsphenamin was made.

January 26. The patient was feverish. Some red blood cells and casts occurred in the urine again. The boy was cheerful and had a good appetite. The enlargement of the lymphatic glands had disappeared.

February 1. Although the nutrition was not yet up to normal and the boy still looked pale and sallow, the general improvement was quite noticeable. He felt fine, ate with good appetite and would no longer stay in bed. He was apparently well and left the hospital at his own request.

The results of the blood examination are shown in Table 1.

Treatment.—Arsphenamin (salvarsan brand) was the specific remedy applied throughout the course of the disease, save that the patient was twice (December 22 and 23) put on injections of 10 c.c. of 10 per cent. gelatin, and infusion of uva ursi was tried for the intercurrent hemorrhagic nephritis. No other medicine was given. Milk was the sole food. The amount taken daily was not over a half liter the first few days. Afterward the amount was increased and finally 1.5 liters was the ration.

Further Course of the Disease.—March 4, the boy visited our hospital again. At that time he was looking well. Considerable improvement in his nutrition had taken place in the course of the two months since his discharge. On examination no remarkable change was found in the pharynx, viscera or lymphatic glands. The orbital tumor, however, was further enlarged and had reached the size of a chestnut. The consequence was a lessening of the upward movement of the eyeball. Another tumor had made its appearance on the left temporal bone. It was hemispherical in shape and as large as a hen's egg. It was not mobile. As regards its nature, it was quite similar to that of the orbital tumor. The senses of sight and hearing were normal.

Outcome.—Following this visit we had no further opportunity to see the patient. Later, we learned from his mother that the boy was almost always lively enough to play around and though he was sometimes feverish, the temperature was never over 38 C. The tumor, however, progressively enlarged and his death occurred at the end of April, 1916. The total course of the malady was about five months.

From the foregoing, some clinical signs of peculiar importance may be noted: The continuous fever, the angina, the glandular enlargement, the hemorrhagic nephritis, the strong diazo reaction in urine, the petechia, the marked leukocytosis, with the appearance of the pathologic myelogenous white cells and the tumors on the skull were the chief evidences of the disease.

A NEW MICROBODY FOUND IN THE CIRCULATING BLOOD

A peculiar microbody was found in the blood some time in the course of the disease, which we think is worth while describing. As mentioned, arsphenamin was used three times in the case, which may have given rise to the appearance of the microbodies. They were observed the first time on the third day after the second arsphenamin injection. Ten days later, when the blood films were examined again, the microbodies were no longer to be found. The second appearance took place on the second day after the third arsphenamin administration, this time also lasting for a few days only. The microbodies were found, five to ten in number, in one field of vision of the fresh blood film made in the usual manner, examined with a $\frac{1}{12}$ oil immersion lens and an ocular 3 Leitz.

Form and Structure of the Microbody.—The bodies were examined in fresh blood films only, as we were not successful in getting stained preparations at that time. They were oval in shape and had a distinct contour (Fig. 2). Although they differed slightly in size, the average measures were from 2.5 to 3.0 and 1.5 to 2.0 microns in length and breadth, respectively. The body consisted of two parts—the protoplasm and two nucleus-like corpuscles. The former was a nontransparent, homogeneous mass of grayish-white color and contained neither granules, pigment nor vacuoles. The corpuscles were glistening masses of round shape and of the same size. They were placed one at each pole of the microbody. Flagella were not to be seen. Every one of the microbodies had almost the same structure. They made neither movement nor changed shape. They were always found outside of the blood cells, free in the plasma (see figure). They were resistant to acetic acid of 0.3 per cent. concentration which was used to destroy the erythrocytes to facilitate counting the leukocytes.

None of the experiments for staining, culturing and transmission to animals of the microbodies was successful. It was peculiar that the bodies could never be stained, though the blood cells were found well dyed on the same film.

Nature of the Microbody.—In discussing the nature of these bodies the first thing to be remembered is that the observations were made with fresh blood films alone. In such a condition it is not necessary to differentiate the microbody from an artificial product which may be formed only when complicated manipulation such as fixing or staining is applied to blood films. Moreover, all of these microbodies were similar to each other in both size and structure and were found merely in a certain stage in the course of the disease. In any other state, whether in health or illness, such a structure has never been observed in the human blood. The microbody, therefore, should not be regarded as an artificial product, but is to be considered as specific to the disease concerned.

Varieties or incidental products of the blood cells formed by arsphenamin influences are next to be differentiated. The microbodies contained no hemoglobin and were resistant to dilute acetic acid as mentioned. Every one of them had a similar structure and form. They could never be stained, while the normal as well as the pathologic white cells were well dyed. From these points, it is fair to consider that the microbody is not the incidental product of either erythrocyte or leukocyte. So far as we know, no blood cell body has been described which has such a structure as that of the microbody.

Although Kurloff-Patella's body in the blood of the normal guinea-pig and the large lymphocyte-containing vacuole observed in a case of

TABLE 1.—Blood Findings

Date	Total Erythrocyte Count*	Total Leukocyte Count	Ratio of Leukocytes to Erythrocytes	Hemoglobin†	Color Index	Polychromatophilia	Differential Leukocyte Count in per Cent.									
							Large Lymphocytes	Small Lymphocytes	Large Mononuclears and Transitionals	Myeloblasts	Promyelocytes	Myelocytes	Metamyelocytes	Polymorphonuclear Neutrophils	Polymorphonuclear Eosinophils	Mast Cells
12/13/15	4,072,000	84,610	48	60	0.74	0.7	6.0	12.0 (18)	9.0	8.0	5.0	13.0	1.0 (27)	44.0	0.7	0.3
12/16/15	3,792,000	88,960	43	60	0.79	0.7	8.0	14.0 (22)	4.0	8.5	8.0	14.0	4.5 (35)	36.0	0.7	0.3
12/21/15	3,020,000	61,120	49	57	0.94	0	5.0	11.0 (16)	8.0	7.5	4.0	19.0	7.5 (38)	34.0	0.3	0.7
12/24/15	2,392,000	49,520	48	50	1.04	0.3	5.0	16.0 (21)	6.0	4.0	6.0	19.0	2.0 (31)	41.0	0.7	0
12/27/15	3,128,000	42,720	73	45	0.72	0.3	2.0	23.0 (25)	5.0	3.0	2.0	18.0	5.0 (28)	41.0	0.7	0
12/31/15	1,992,000	27,360	73	47	1.18	0	4.0	30.0 (34)	8.0	1.5	2.5	14.0	4.0 (22)	34.0	1.0	0
1/17/16	1,832,000	10,880	168	38	1.04	0	6.0	45.0 (51)	8.0	2.0	2.0	3.5	0.5 (8)	32.0	1.0	0
1/24/16	2,544,000	19,040	133	50	0.98	0	8.0	37.0 (45)	5.0	3.0	1.5	5.0	0.5 (10)	38.0	1.0	0

* Thoma-Zeiss' hemocytometer was used.
† Sahli-Gower's hemoglobinometer was used.

acute leukemia by Pappenheim and Hirschfeld[1] were reported, either of them is nothing but the leukocyte itself. They differ entirely from our microbody either in size, in structure, or in staining properties, so that it is now beyond question that the microbody does not belong to such a varietal form of leukocyte.

Accordingly, it seems to be justifiable at last to consider the microbody as a parasitic organism in the blood. It, indeed, must be a new parasite, because in comparison with the known parasitic protozoa and yeasts, none of them is related to the microbody in any point; and furthermore, Hoefer's,[2] Loewit's,[3] Pappenheim's[1] and Kopanaris'[4] corpuscles are quite different from ours.

The nature of leukemia and the associated diseases is unknown. Some authors regard leukemia as related to the malignant tumor, but there are few adherents to that opinion. On the other hand, the disease, especially its acute form, resembles more an infection, which gives rise to pathologic hyperplasia of the leukoblastic tissues. Various organisms have been described, but nothing specific has been determined. Owing to the consideration, however, that the streptococcus or staphylococcus plays often a certain important part in the etiology of acute leukemia, some authors, such as Sternberg,[5] Pappenheim,[6] Lehndorff,[7] Ziegler and Jochmann[8] and Luedke,[9] regard the disease as being caused by the specific reaction of the hematopoietic tissues against the septicemic process in a certain individual constitution, and subsequently they suggest that it is not necessary to have to determine a specific virus for the genesis of leukemia.

Although our microbody is probably a new parasite and may have a certain etiologic meaning as discussed in the foregoing, we do not yet insist on regarding this body as the sole causative factor of the disease. Nevertheless, we think it is proper to consider that this parasite acts as an exciting cause of the disease, the essential part of the etiology being existent in the peculiar disposition of the hematopoietic system.

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1. Pappenheim and Hirschfeld: Folia haemat., 1908, **5,** 361.
2. Hoefer, P. A.: Centralbl. f. Bakt. u. Parasitenk., Orig., 1910, **55,** 19.
3. Loewit, M.: Die Leukaemie als Protozoeninfektion, Wiesbaden, 1900; Ztschr. f. Heilk., Abt. f. path. Anat., 1900, **21,** 280; Ibid., 1901, **22**; Ziegler's Beitr. z. path Anat. u. z. allg Path., 1903, **33,** 113; Centralbl. f. Bakt. u. Parasitenk., Orig., 1908, **45,** 600.
4. Kopanaris: Arch. f. Schiffs- u. Tropen-Hyg., **16,** 313.
5. Sternberg, K.: Wien. klin Wchnschr., 1911, No. 47.
6. Doehrer and Pappenheim: Folia haemat., 1913, **16,** 145; Pappenheim and Hirschfeld: Ibid., p. 368; Pappenheim: Ztschr. f. exper. Path. u. Therap., 1914, **15,** 39.
7. Lehndorff, H.: Jahrb. f. Kinderh., 1910, **72,** 53.
8. Ziegler and Jochmann: Deutsch. med. Wchnschr., 1907, No. 19, p. 749.
9. Luedke, H.: Deutsch. Arch. f. klin. Med., 1910, **100,** 553.

EFFICACY OF ARSPHENAMIN ON ACUTE MYELOGENOUS LEUKEMIA

Arsphenamin has been employed in the treatment of chronic leukemia by several authors, but the effect has not been striking in any case, except that of Ireland,[10] who claimed to have obtained some improvement of the disease through the remedy. As regards the influence of arsphenamin on an acute form of leukemia, no report suggesting its curative value has ever been published.

Using arsphenamin in our case of acute myelogenous leukemia, a marked apparent recovery was observed both in the general and the local symptoms. The patient, who looked like one suffering from a severe form of scarlet fever on admission, got three successive injections of the remedy which, as noticed elsewhere, was the sole specific treatment employed in the case. The effects were so remarkable that the fever, which had been as high as 39 C., made a gradual decline to the subfebrile point, the appetite returned and the boy became lively again. Furthermore, the hemorrhagic nephritis was cured, the diazo reaction disappeared and the subcutaneous bleeding also ceased. The swelling and the injection of the pharyngeal mucous membrane were gone, so that difficulty in swallowing and breathing disappeared and the soreness in the throat was no longer felt. The enlarged lymphatic glands became reduced markedly in size. Thus, all of the acute symptoms of the disease were almost perfectly dissipated by the arsphenamin.

The efficacy of arsphenamin in leukemia is to be demonstrated more directly in the change of the blood constitution. As regards our case, a remarkable improvement, not only in quantity, but also of quality, occurred in the state of the colorless corpuscles. The total number was decreased from 80,000 to 10,000. The young type of leukocytes, which had been ranging from 27 to 38 per cent. before treatment, were reduced gradually in number to reach, finally, 8 to 10 per cent. of the total leukocytes. Accordingly, the blood picture more closely approached that of the normal state. Although it was not possible to drive all of the pathologic leukocytes out of the blood current, and some of them were left, these were so few that they scarcely made up more than one-twelfth to one-thirty-fifth of the initial count. On the contrary, the lymphocytes were increased from 18 per cent. to 45 per cent. The latter figure approximates the normal standard of this kind of white cells at the age of the boy referred to. The differential count of the physiologic granulocytes also became normal.

It is therefore to be concluded that arsphenamin produced the most noticeable influence in a curative sense on the white cells. As regards

10. Ireland, Baetjer and Ruhräh: Jour. Am. Med. Assn., 1915, **65**, 948.

the red blood cells, they were greatly lessened. This quantitative diminution, however, should not be considered as indicating an aggravation of the leukemic process. The anemia occurring in the course of leukemia is usually regarded as due to the diminishing productive function of the erythroblastic tissue, which is induced by an excessive proliferation of the leukoblastic elements of the blood-making organs.

As to the cause of the pallor in our case, however, such an explanation as the foregoing is not to be applied, for the changes brought about in the state of the colorless corpuscles suggested that the hyperplastic process which had been raging in the leukoblastic tissue was no longer in progress, or it was, rather, diminished through the treatment. The actual etiologic factor of moment, therefore, was to be found in the serious bleedings themselves which came on in the course of the disease. Besides the complication of nephritis, the diminished erythroblastic function as a result of the general weakness caused by the nutritive deficiency due to the long continuance of the sole milk diet and the intensified destructive process of the red blood cells as a general phenomenon in the course of a febrile disease, were also to be considered to have played important parts in inducing anemia in our case.

Notwithstanding the therapeutic use of arsphenamin, which resulted in the disappearance of most of the symptoms of the disease, the tumor growths occurred in the skull, as mentioned in the history. On account of this, however, the curative value of the remedy should not be doubted.

Recovery in leukemia and chloroma is practically unknown. The cases reported by Tuerk[11] and by Luedke,[9] in which they claimed to have observed a certain recovery, belong to the exceptions. Although a curious remission may occur spontaneously in leukemia, the acute form of the disease runs a malignant course steadily, to reach a fatal outcome in a short time. Accordingly, the marked improvement extending over a considerable period, and, developing soon after the application of arsphenamin, as in our case, should not be regarded as being produced by the influence of the remedy.

Occasionally the disappearance of some of the leukemic symptoms may occur when septicemia comes on in the course of the malady. In such a case, however, owing to the complication itself, the general condition of the patient becomes worse and early death ensues, so that any remission can never be observed.

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11. Tuerk: Wien. med. Wchnschr., 1907, p. 939.

MODE OF ACTION OF ARSPHENAMIN ON THE DISEASE IN INDUCING THE DIMINUTION OF LEUKOCYTES

From the foregoing it is evident that the influence of arsphenamin was most remarkable in improving the state of the colorless corpuscles. It now remains to discuss the mode of action of the remedy in causing this hematologic change. The lessening of the leukocytic count may be brought about in one of the following ways:

Uneven distribution of leukocytes in the body, which occurs while the majority are retained in some of the inner organs and the remainder only are left free in the blood current, may be the cause of the lower count of the cells in the peripheral blood vessels. That this is not true is shown by the fact that there is no evidence of a similar process in any other disease under treatment with arsphenamin, and also by the fact that arsphenamin undergoes steady excretion from the time it is introduced and is not kept in the body in such a sufficient quantity as to exhibit its activity continuously for such a long period as occurred in our case; and moreover, the marked relief of various other symptoms does not suggest the justifiability of such an explanation. The diminution of the leukocyte count, therefore, is to be regarded as a result of an actual decrease in number in the whole circulatory system and not of their uneven distribution in the body.

The change in the blood picture may be induced by an abnormally increased activity of the leukocytolytic process. But that this was not the case is proved by the result of the investigation of the purin metabolism. Applying the method of Hopkins-Woerner, the routine analysis of the urine regarding uric acid was carried out. The patient was fed on a purin-free diet — milk alone — with the purpose of estimating the endogenous purin excretion. The chart and Table 2 show the result of the analyses. Uric acid is estimated in amount of excretion in twenty-four hours.

In the acute and malignant stage, in the early course of the disease, uric acid was estimated at the amount of not exceeding 0.279 gm. per day. Later, even when the transitory recovery from the disease as the result of the arsphenamin injections and the lessening of leukocytes occurred, the excretion of uric acid was not increased, but reduced to such a small amount as less than 0.05 gm. This shows that the destruction of leukocytes was not beyond the normal, or rather was decreased.

The same conclusion may be made from the hematologic point of view. If the leukocytolytic process be active in an organism, the consequence is the appearance of the young types of the white cells in a considerable number in the blood current, provided the hematopoietic function is kept in maintenance. On the contrary, in our case, the

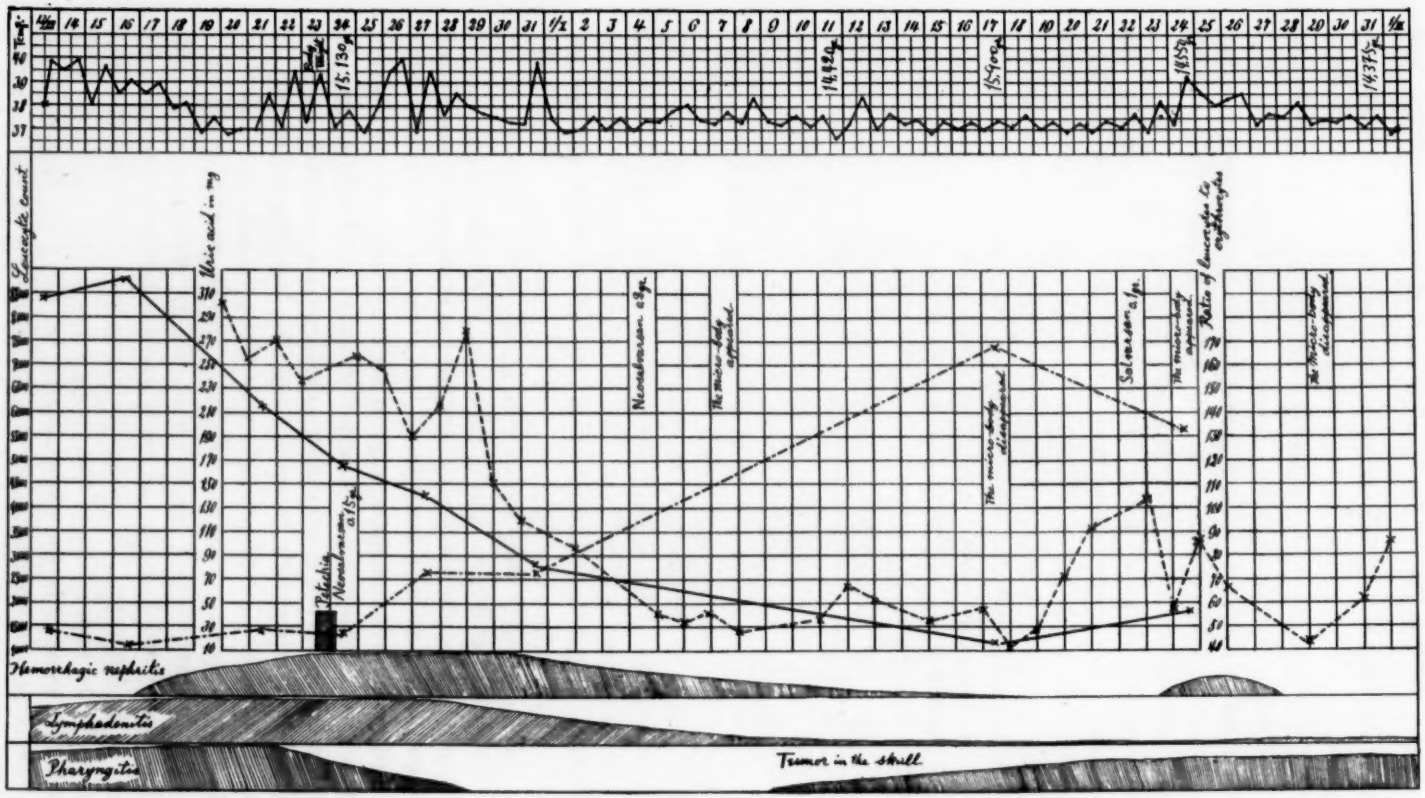

Fig. 1.—Diagram showing the chief symptoms, the blood findings and the amount of uric acid excreted. ——— leukocytes; —.—.—.— ratio of leukocytes to erythrocytes; — — — — amount of uric acid.

TABLE 2.—URINE

Date	Amount in C.c.	Specific Gravity	Albumin	Deposits				Uric Acid in Mg.
				Erythrocytes	Leukocytes	Tube Casts	Epithelium	
12/19/15	590	1.008	±	—	—	—	—	297
12/20/15	400	1.009	±	—	—	—	—	252
12/21/15	490	1.011	+++	+++	+	—	—	270
12/22/15	460	1.011	+++	+++	+	++*	—	233
12/23/15	1,040	1.006	+++	+++	+	++*	—	250
12/24/15	500	1.004	+++	+++	+	++*	—	254
12/25/15	410	1.015	+++	+++	+	++*	—	245
12/26/15	280	1.010	+++	+++	+	++*	—	190
12/27/15	300	1.015	+++	+++	+	++*	—	213
12/28/15	750	1.012	+++	+++	+	++*	—	277
12/29/15	420	1.017	+++	+++	+	++*	—	150
12/30/15	680	1.013	+++	+++	+	++*	—	120
12/31/15	...	.....	.....	.....	.....	.....	.....	...
1/ 1/16	830	1.009	+++	.....	.....	.....	.....	95
1/ 2/16	470	1.014	+++	.....	.....	.....	.....	176
1/ 3/16	960	1.011	+++	++	—	++*	—	...
1/ 4/16	820	1.011	+++	++	—	++*	—	37
1/ 5/16	840	1.010	+++	++	—	++*	—	33
1/ 6/16	870	1.010	+++	++	—	++*	—	44
1/ 7/16	810	1.011	+++	++	—	++*	—	25
1/ 8/16	860	1.014	++	.....	.....	.....	.....	...
1/ 9/16	690	1.014	++	.....	.....	.....	.....	...
1/10/16	980	1.007	++	—	++	++	—	33
1/11/16	1,155	1.007	++	—	++	++	—	65
1/12/16	950	1.009	++	.....	.....	.....	.....	53
1/13/16	920	1.010	+	.....	.....	.....	.....	...
1/14/16	730	1.008	+	.....	.....	.....	.....	43
1/15/16	770	1.010	±	.....	.....	.....	.....	35
1/16/16	810	1.010	±	—	+	—	—	45
1/17/16	830	1.007	±	—	—	—	—	15
1/18/16	840	1.008	—	—	—	—	—	24
1/19/16	730	1.010	—	.....	.....	.....	.....	74
1/20/16	840	1.008	—	.....	.....	.....	.....	113
1/21/16	860	1.009	—	.....	.....	.....	.....	...
1/22/16	900	1.009	—	.....	.....	.....	.....	135
1/23/16	830	1.008	—	.....	.....	.....	.....	42
1/24/16	840	1.008	+	.....	.....	.....	.....	103
1/25/16	820	1.008	+	.....	.....	.....	.....	60
1/26/16	1,100	1.007	+	+	+	+	—	..
1/27/16	710	1.008	+	.....	.....	.....	.....	...
1/28/16	790	1.008	—	—	—	—	—	15
1/29/16	920	1.007	—	.....	.....	.....	.....	...
1/30/16	1,010	1.008	—	.....	.....	.....	.....	54
1/31/16	760	1.008	—	.....	.....	.....	.....	104

* Granular.

count of the young types of leukocytes became less, in spite of there being no decrease of the blood-making activity in the tissues, as is suggested by the leukocytic picture.

Accordingly, it is most probable that the striking improvement of leukocytes, both in form and number, is due to the inhibition of the leukoblastic function, especially of the myelogenous white cells, which is caused either through the direct influence of arsphenamin on the hematopoietic organs, or indirectly as a result of the primary germicidal action of the remedy.

SUMMARY

A case is reported of acute myeloblastic leukemia accompanied by chloroma-like tumor growths in the skull, occurring in the course of the disease.

Arsphenamin was used in three injections, which resulted in an astonishingly good effect in causing the cessation of all of the leukemic symptoms, with the exception of the gradual enlargement of the tumors. The improvement in the blood findings was very remarkable.

In consequence of the arsphenamin treatment, a great number of peculiar microbodies made their appearance in the blood. The nature of these bodies was not determined, but it is considered justifiable to regard them as a new variety of parasitic micro-organism of a certain pathogenic significance in this case of leukemia.

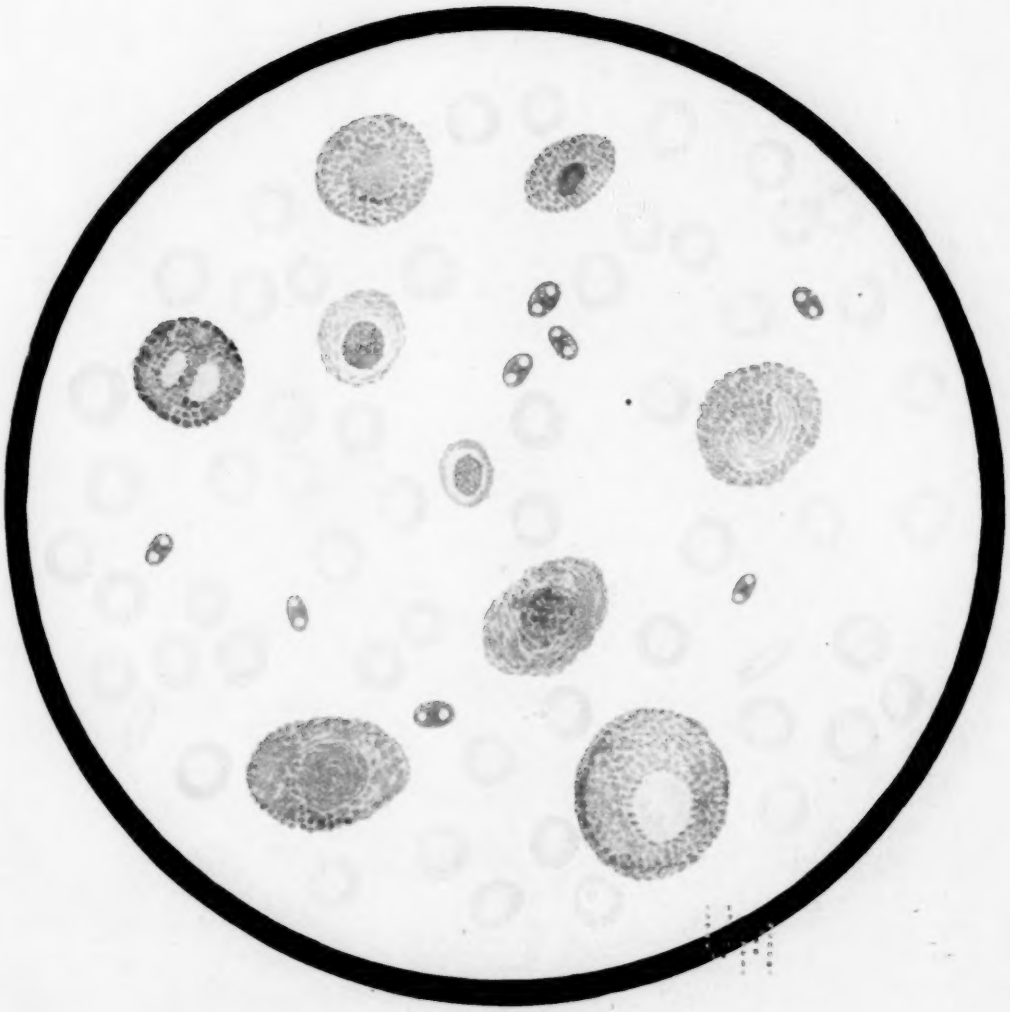

Fig. 2.—Blood film preparation showing the new microbodies.

Illustrating Article by Itsuyoshi Inaba, M.D., and Shin Ohashi.
American Journal Diseases of Children, July, 1918.

A CLINICAL CONSIDERATION OF MACEWEN'S SIGN

ESPECIALLY WITH REFERENCE TO ITS USE IN POLIOMYELITIS *

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In a previous article[1] on the hydrocephalus of poliomyelitis we frequently referred to Macewen's sign and endeavored to emphasize its importance in the detection of this condition. The great clinical importance of the sign, its ever widening field of applicability, its relative certainty as an index of the existence of acute hydrocephalus, the simplicity of the methods for its detection and the absence of any detailed description of it in our present day treatises on physical diagnosis were the incentives to the writing of the present paper. The classical description of Macewen will be first summarized, the later study of the subject by Wilcox will be reviewed, and an endeavor will be made further to establish the value of the sign in physical diagnosis.

Macewen of Edinburgh first described the sign. He employed it in the diagnosis of brain tumor and abscess over a period of ten years and found it distinctly useful. Quoting more or less directly from his original description,[2] he says:

The percussion note is produced by the vibration of the cranial walls when struck and is modified by the consistency and the volume of the contents and their relative position to the bone. When struck a thin skull vibrates more readily than a thick one; indeed, a skull may be so thick that it vibrates little if at all to ordinary digital percussion. The note obtained in healthy adults is generally high pitched, imparting the idea of solidity; in many adults, in fact, the bones of the cranium are too thick and dense to permit active vibrations. In the cranium of a normal infant, whose bones are only united by membranes, the sound obtained is so dull and flat as scarcely to be perceptible. Should the contents of such a cranium, however, increase sufficiently to produce tension the note becomes clear. In healthy children, in whom the ordinary density, consistency, and relation of healthy brain to the

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* Read before the Pediatric Section of the Kings County Medical Society, Oct. 22, 1917.

1. Regan, J. G.: The Hydrocephalus of Poliomyelitis, Am. Jour. Dis. Child., 1918, **15**, 259.

2. Macewen, W.: Pyogenic Infective Diseases of the Brain and Spinal Cord, Glasgow, 1893, p. 146.

cranial bones exist, a dull note is produced on percussion, but where the contents are more fluid the bones will vibrate more readily and a clearer percussion note will be obtained. A somewhat clear note is sometimes encountered in children who have the typical enlarged head associated with infantile rickets, but the change in note is not constant, and some of these rachitic children with a positive sign have been afterwards proved to have ventricles distended with fluid. When the lateral ventricles are distended with fluid the percussion note is markedly altered, the resonance being greatly increased. The exact musical quality of the note is difficult to describe, but it conveys the idea of hollowness. Macewen further says that he observed to a conclusion ten cases with a positive sign during life, in whom frozen transverse sections of the brain were made post mortem, all showing distended ventricles, with thinning of the brain substance. He considered the upright position most suitable for eliciting the sign, and for percussion employed either the tip of the middle finger or the ordinary instruments used in percussing the chest. He believes the pterion or a little posterior to that point to be the best place to elicit the sign. He also makes mention of the fact that the ear of the investigator may be placed in contact with the head of the patient and the note determined in this manner. Special emphasis is placed on the change in the percussion note at one particular spot according to the position of the patient's head. In most cases the eliciting of the percussion note did not seem to incommode the patients and in many instances the children were amused. The sign was present in forty children and young adolescents having distended ventricles arising from many different causes.

The original description of Macewen was later partly reviewed by Wilcox in an article[3] in which he undertook the difficult task of giving some of the basic principles underlying the question of skull percussion. At the same time he described a new auscultatory percussion method for eliciting the sign. This method consisted of the application of the stethoscope to the forehead just above the base of the nose, after which the skull is tapped directly over the parietal region, beginning over the parietal boss and progressively approaching the point at which the stethoscope is applied. This should be carried out on both sides of the head. The typical sign consists in a high-pitched, short, cracked-pot note. It is most distinct when percussion is being performed over, behind or below the parietal boss, is unchanged as the point percussed passes downward, and diminishes in intensity and character as the percussing finger approaches the stethoscope. The reverse of this occurs when percussing the normal skull, owing to the fact that nor-

3. Wilcox, H. B.: Arch. Pediat., December, 1915, p. 909.

mally vibrations are better conducted along the bony wall than through the brain and meninges.

Wilcox noted the presence of a positive Macewen sign in children with serous meningitis complicating gastro-intestinal disturbances, pneumonia, typhoid fever and influenza; also in various acute infections of the meninges, especially tuberculous meningitis and poliomyelitis. He found it to be absent in congenital hydrocephalus. He remarked the reduction in the intensity of the sign which may follow lumbar puncture with the removal of varying quantities of spinal fluid, and he considered the sign of value in estimating the necessity for repeated rachiocentesis.

Heiman and Feldstein[4] and Sophian[5] make frequent reference to the presence of Macewen's sign in cases of meningococcus meningitis, the former authors noting it in thirty-five out of forty-five of their patients who were over 2 years of age. Koplik also draws attention to its use in tuberculous[6] and epidemic meningitis,[7] noting it in thirty-four of fifty-two cases of the former disease, and stating that it may appear comparatively early. Neal and Du Bois[8] in a varied and extensive experience with meningeal conditions lay emphasis on the fact that whenever they have found the Macewen sign they have always obtained increased fluid, except in cases of postbasic meningitis.

There is no doubt that the authorities cited have had exceptional opportunity to observe cases in which the value of this sign could be carefully judged, and they all uniformly agree on its decided clinical importance; yet there has been for some time, and there still remains, a general skepticism among a great many members of the medical profession regarding it. This is due in some instances to lack of opportunity to make use of the sign in a sufficiently large number of suitable cases at one time, and no doubt also to the fact that there is at present no true classification of skull percussion.

In order to explain the basis for the existence of the sign in poliomyelitis the gross pathologic picture of the changes in the brain which occur in that disease must be considered. As explained in the aforementioned article[1] under the pathology of the edema of poliomyelitis, the lateral ventricles are often definitely enlarged post mortem. During the early, acute stage of the malady this enlargement is due to distention as a result of the increased formation, diminished excretion

4. Heiman, H., and Feldstein, S.: Meningococcus Meningitis, New York, 1913, p. 138.

5. Sophian, A.: Epidemic Cerebrospinal Meningitis, St. Louis, 1913, p. 59, 70, etc.

6. Koplik, H.: Quoted by Brown, in Osler and McCrae's System of Medicine, New York and Philadelphia, 1913, **1,** 423.

7. Koplik, H.: Med. Rec., New York, 1906, **70,** 481.

8. Neal, J., and Du Bois, P.: Am. Jour. Dis. Child., 1915, **9,** 1.

and resultant accumulation of the cerebrospinal fluid. The soft, yielding tissue of the cerebral hemisphere is thus compressed between the unyielding calvarium and the distended ventricles. This gives an entirely different relation to the tissues within the cranial cavity, passing from without inwards, as compared with that which exists under normal conditions. Normally on cross section through the skull we should expect to find first the cranium, beneath this and intimately attached to it the dura mater, then the subdural space, then the arachnoid, and beyond this the subarachnoid space, and finally the pia mater closely investing the surface of the brain. The subarachnoid space contains connective tissue trabeculi and a quantity of cerebrospinal fluid, and while not large, yet it is a definite area, and is of a sufficient size to keep the surface of the cerebrum from coming into close contact with the arachnoid, and hence indirectly with the dura and calvarium (the subdural space being usually so small as to be negligible, and the arachnoid and dura lying almost in contact). With the distention of the ventricles and the edematous swelling of the brain tissue that occur with the onset of poliomyelitis, the subarachnoid space is partially, or more usually completely, obliterated—the spinal fluid being displaced into the larger cisternas—the membranes are crowded together, the brain is brought into more or less immediate contact with its bony covering, and the tension of the contents of the cranial cavity is raised.

It is a recognized fact that in percussion of the lungs when the tension of the pulmonary tissue increases, the resonance becomes more marked. So it is with percussion of the skull—the greater the tension of the cranial contents the more resonant is the quality imparted to the note. Under normal conditions, with the relation of the cerebral contents as previously described, the sound obtained in the frontal and parietal regions is of a dull character and closely resembles that produced by tapping on a thick and not too resonant board. It is a somewhat similar sound to that heard on percussion of any bony surface (except that it is not quite so flat), and is very little influenced by the cranial contents. When analyzed into its component parts it is found to be of high pitch, short duration, slight intensity and resonance. With the increase in intracranial tension, however, the brain closely crowded against its bony envelope, the subarachnoid and the subdural spaces practically abolished, the percussion note becomes decidedly changed in its quality, the vibrations set up in the bone now being easily and directly transmissible to the underlying tissues, giving origin to a new sound. As is the case in pulmonary percussion, this note is of a more resonant character and of a greater intensity, longer duration, but of a lower pitch than the normal note just described. The quality of the sound may be best described, as was done originally by Macewen, by saying that "it conveys the idea of hollowness." Sometimes also it

gives the impression of fluid, the more so the younger the child. It is an entirely different sound to that obtained on percussion of any other part of the body. It is best imitated by loosely clasping the fingers with the palmar surfaces opposite but not touching, and then quickly bringing the latter together with moderate force. Some of its qualities are also manifest when forcible percussion is made over a pulmonary cavity with the mouth open.

As we would expect, hydrocephalus may be of various degrees and thus the same sound would not be obtained over a skull in which the ventricles were only slightly distended, and the subarachnoid space only partially obliterated as when the ventricles were markedly distended and the cerebral hemispheres compressed against the bone. In the former instance the note would only be slightly influenced by the cranial contents, while in the latter it would be markedly so. Hence there may be said to be varying degrees of the positive Macewen. Arbitrarily it is best to divide the sign into slight, moderate and markedly positive. The last being identical with the typical sound already described, and the first of a slightly lower pitch, but greater resonance, as well as longer duration than the normal skull percussion note; a moderately positive sign attains a medium between the two.

In recognizing the positive sign, two elements must be considered, namely, the auditory and the tactile. The auditory quality we have just described; but the tactile element is also of importance in the proper interpretation of the sound produced, for there is almost as much change conveyed to the finger on tapping the skull as there is in the sound heard by the ear. It is truly difficult to describe this tactile element because we have no means of dividing it into its various characteristics as we have in the case of sound. There is an appreciable change, however, which the finger by practice will learn to detect. Normally on percussing the skull the impression the finger receives is of a hard, bony, nonresonant, resistant, and unyielding surface, the retention of the vibrations by the bony envelope of the skull being definitely appreciated. With the ventricles distended with fluid, the impression conveyed is distinctly different, in that the vibrations set up are felt to be transmissible to the contained tissues, and the percussed surface feels less resistant and unyielding than previously. This element of the sign is more appreciable in young children than in adults, or adolescents, and, in fact, in the latter two it is usually entirely lacking, owing to the thickness of the calvarium. We believe it is principally the presence of this tactile element in the former class of patients and its absence in the latter which makes Macewen's sign so much more valuable in children.

In eliciting the sign in the routine physical examination of patients with poliomyelitis—and this applies to any other acute meningeal con-

dition as well—we have made use of Macewen's original method, with the exception that of necessity we have employed the recumbent posture, owing to the pain usually produced by any attempt to have the patient sit up during the early, acute stage of the disease. This position has, however, proved perfectly satisfactory in every respect. The method used has been as follows:

The pillow is removed from under the child so that the head lies on an even surface; the head is turned first to one side and percussion is carried on over the region of the parietal eminence which is lowermost, after which the position of the head is reversed and a similar area on the opposite side is percussed. It is often preferable to remove the child from the crib and lay it on a wooden table with a thin pillowslip folded beneath the occiput. It is essential that the room in which the examination is made be quiet, and that the examiner, by bending, bring his ear close to the child's head while the percussion is being carried out. Gentle tapping with the tip of the middle finger is just as effective in bringing out the note as hard loud blows with the finger or a percussion hammer. The use of the latter instrument is open to the decided objection that it prevents the determination of the tactile quality of the sign.

The pterion was the point originally specified by Macewen for best eliciting the sign. We have also used this area in a great many cases, but by comparison have found that the regions of the parietal eminences are just as suitable, if not more so, especially, since the parietal bone in that location is not covered by muscular tissue. In order to facilitate the determination of the degree of the positive sign it is often useful to percuss the skull from behind forward, starting at the lambdoid suture and ending just behind the frontal eminence, following a line which would be just superior to the upper temporal ridge and which passes through the parietal boss. If a marked Macewen's sign is present the typical sound will usually be elicited over most of the entire area percussed; with a moderate or slightly positive sign, the sound will be proportionately more localized to the parietal eminences or to the pterion.

The percussion-auscultatory method of Wilcox has been employed often in our cases, but mostly in a confirmatory way when the sound obtained on percussion is of an indefinite character. In children we have not found it as reliable as the original method, lacking as it does the tactile element. In adolescents and adults it is probably of more value, as percussion often shows very little or no change of note in these patients, owing to the thickness of the cranial walls despite the fact that symptoms of distinct hydrocephalus exist. It is difficult to state just how much more accurate the method of Wilcox is in such cases without a more extended study, but we believe that it may often be found to be distinctly superior. In these older patients, also, it is necessary to emphasize the fact that Macewen's sign must not be relied on too strictly as an index for the treatment of hydrocephalus by rachiocentesis. The other symptoms must here be taken into consideration. Thus, an elevated temperature, rigidity of the neck or limbs, hyperesthesia, drowsiness or stupor, rapid pulse, dilated pupils, sweating, and irregular vasomotor, flushings of the skin, and, if possible, the findings on the examination of the eyegrounds should be the guiding

factors rather than the apparent presence or absence of Macewen's sign.

A few factors may slightly interfere with the test even in children. Thus, in the case of colored patients we have often found it relatively unreliable, due no doubt to the frequency of rickets in that race. Then again, a large growth of hair renders difficult direct percussion of the skull and the sound obtained is materially changed. This is simply remedied by clipping the hair, or, if necessary, shaving the scalp. Diseases of the bones, especially rickets, as Macewen and Wilcox have remarked, may falsely simulate a positive sign. Thus various factors must be considered which will cause some deviation from the normal note without there necessarily being a hydrocephalus present. Allowance can usually be made for them, however, as they are readily recognized and rarely interfere to such a serious extent as entirely to disguise or simulate a marked Macewen's sign.

During the 1916 epidemic of poliomyelitis we had ample opportunity to use this sign and to test carefully its value in 1,798 cases in the hospital. We could not help but be impressed by its importance, affording, as it does, a definite physical sign by means of which a diagnosis based on the other symptoms of suspected hydrocephalus may be confirmed and treatment by lumbar puncture instituted. We wish to emphasize its nearly constant value in this particular regard, because at present lumbar puncture would seem to be one of the most important procedures in the treatment of this disease. It is probably encountered more frequently in poliomyelitis, and is more marked than in any other acute disease with the exception of tuberculous meningitis. It is this common occurrence that makes its use in the physical examination of a patient with the former disease of vital importance. Macewen's sign was present in all cases seen in the preparalytic stage of the malady, and was usually of a marked degree. It was also extremely frequent in the early paralytic period of the disease, being present to some extent in over 80 per cent. of the patients, and in some cases, especially of the respiratory type, it persisted for as long as from three to eight weeks after the onset.

The degree of the positive sign was usually proportionate to the pressure and quantity of spinal fluid removed on lumbar puncture. Unfortunately, as spinal fluid pressures were not taken on the cases in which this was noted, and since the estimations of pressure were based on the rate of flow through the needle in a given period of time, the first fact cannot be scientifically proved, yet the clinical impression received by the rough method of estimation used was that a distinct relationship existed, as is shown in the accompanying table. Thus, if Macewen's sign was marked, the fluid was usually under marked pressure, spurting from the needle as soon as the stilet was with-

drawn, while if it was slight the fluid would merely flow away rapidly. The relation between the positive sign and the quantity of fluid removed was more easily proved as the table referred to shows.

Wilcox noted a change in the percussion note after the removal of various amounts of spinal fluid. This is what would be looked for if the quantity withdrawn were sufficiently large. It seems hardly likely, however, that the removal of a small amount, say from 5 to 10 c.c., would materially influence the sound; but when larger quantities, from 20 to 30 c.c. or over, are withdrawn, the rate of normal flow (20 drops per minute) being approximated before the needle is withdrawn, the relative position of the contents of the cranial cavity to the bone may be affected to such an extent that a change in the tissue conduction would result and a different note be obtained. This change has been observed very often in our cases following rachiocentesis. The table shows the relation between the positive sign before and after puncture, and the quantity of fluid removed. It demonstrates also that, while a definite relationship exists between all these various factors—of pressure and quantity of spinal fluid, on the one hand, and the degree of the positive Macewen with subsequent change following puncture, on the other—this relation is not of a constant character, for exceptions are not infrequent. The probable explanation of these variations to the rule is attempted in the footnotes at the end of the table.

It is important to remember that a bulging anterior fontanel in an infant has the same significance as a positive Macewen's sign. Many authors consider that the sign is never present if the fontanel is protruding. This does not hold true so far as we could determine for the hydrocephalus of poliomyelitis, nor for that of tuberculous meningitis, and we feel that there is grave reason to doubt it in ventricular distention from other causes. It seems to us it is merely a matter of what a positive Macewen's sign is considered by the individual writer to be. If only the typical note be considered as a Macewen sign, then truly it is rarely present in infants with a bulging fontanel; but we believe that the sound often elicited in cases of extreme hydrocephalus, in which the fontanel is still patent and bulging, is also a Macewen in the true sense of the word, because it indicates a condition of hydrocephalus just as definitely as does the protrusion of the opening. The sound obtained in these cases differs from the typical note, in that it is of a higher pitch, lower resonance and shorter duration, and in that the tactile element is more prominent and more diagnostic. That a Macewen may exist at the same time as a protruding anterior fontanel is certainly a reasonable supposition when consideration is given to the fact that a moderate degree of ventricular distention may produce a tense and bulging opening, while a greater degree will also alter the relation between the cranial bone and its contents, crowding the latter

MACEWEN'S SIGN TABLE OF AUTHOR'S CASES

Case Number	Date Admitted to Hospital	Age, Years	Date of Puncture	Amount of C. S. Fluid, C.C.	Pressure of C. S. Fluid	Degree of Positive Macewen's Sign	
						Before Puncture	After Puncture
2797*	8/18	2	8/20	28	Moderate increase	Absent	Absent
1867	7/26	2½	8/1	20	Marked	Moderate	Moderate
			8/3	35	Moderate	Moderate	Moderate
			8/4	40	Marked	Marked	Moderate
			8/10	35	Moderate	Moderate	Slight
1756	7/22	4	7/24	32	Moderate	Moderate	Slight
2210	8/5	1½	8/12	35	Moderate	Marked	Moderate
2783*	8/18	1½	8/18	20	Not given	Slight	No alteration
2790*	8/18	5	8/18	15	Normal	Slight ?	No alteration
3088	9/5	7	9/5	26	Slight	Moderate	Slight
2733	8/16	2	8/18	40	Marked	Marked	Moderate
2858*	8/20	2	8/21	15	Slight increase	Slight	Slight change, hardly noticeable
2655	8/15	2	8/17	25	Slight to moderate increase	Slight to moderate	Slight
2710*	8/16	5	8/16	15	Slight increase	Marked	Marked
2909	8/23	1⅓	8/23	34	Marked increase	Marked	Moderate to slight
1869	7/26	7/12	7/29	38	Marked increase	Bulging anterior fontanel moderate	Fontanel tense but not bulging; Macewen absent
3132	9/12	4	9/12	32	Moderate increase	Moderate	Moderate to slight
2745	8/17	3	8/19	40	Marked	Marked	Moderate to slight
2993	8/28	2	9/19	40	Marked	Marked	Slight
2987	8/27	1⅓	8/28	30	Moderate	Moderate	Moderate to slight
3202	9/21	3	10/8	30	Moderate	Moderate	Moderate to slight
1496	7/4	11/12	7/5	30	Moderate	Slight Macewen anterior fontanel bulging	Macewen absent; fontanel slightly tense
3003	8/28	⅔	8/28	68	Very marked	Fontanel bulging; Macewen marked	Fontanel slightly depressed; Macewen absent
2801	8/18	3	8/18	40	Marked	Moderate	Moderate
			8/20	40	Marked	Marked	Moderate
3160*	9/15	1⅔	9/15	18	Slight increase	Marked	Marked

* Case 2710 shows a marked Macewen with all the accompanying evidences of hydrocephalus, yet on puncture only 15 c.c. of fluid were obtained under no pressure over the normal. A case of a somewhat similar character is No. 3160. In such instances it would certainly incline one to think that the edematous condition of the nervous tissue may become so marked, that the foramina of communication between the ventricles of the brain and the subarachnoid space of the cord may be partially and temporarily occluded, thus interfering with the usual circulation of cerebrospinal fluid.

Case 2790 showed a Macewen's sign which was doubtful; the spinal fluid was under normal pressure and no change was noted in the sign after puncture. Probably the sign would best have been called negative in the first place.

Cases 2858 and 2783 exhibited a slightly positive Macewen, 15 c.c. of fluid were removed under very slight pressure, flowing very slowly, little or no alteration in the sign was noted. This is what is usually encountered where the amount of fluid removed is so small as not to influence materially the relative position of cranial vault and its contents to one another.

Case 2797 showed no Macewen and yet the fluid was under moderate increased pressure and 28 c.c. were easily obtained. Probably here it was more a question of some physical changes in the bony envelope which interfered with proper conduction.

closely against the former and increasing the bone conduction so that a new note is produced on percussion.

It was not uncommon to see distinct evidence of pain exhibited on percussion of the skull. Thus, if the examination was carried on while a child was sleeping, he would frequently awaken and begin to cry; or in a stuperous case, the percussion would often arouse the patient to such an extent that he would show evident disapproval of its further use. In children old enough to talk, it was common to have them say that their head hurt and ask to be let alone. That this procedure should be painful during the early, acute period of the disease is not surprising when the severe degree of meningeal inflammation commonly present is considered.

While the subject of this paper has been purposely limited mostly to a consideration of Macewen's sign in poliomyelitis as utilized during the epidemic of 1916 at the Kingston Avenue Hospital, it would seem advisable to say that in subsequent studies we have found this sign equally as valuable in the detection and treatment of the hydrocephalus accompanying tuberculous and cerebrospinal meningitis and the various forms of meningism complicating the infectious diseases.

THE CURATIVE AND PROPHYLACTIC VALUE OF VACCINES IN PERTUSSIS*

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At present there is considerable difference of opinion as to the value of vaccines in the treatment of disease. It may be said, perhaps, that there is a tendency to grant them a less important position in therapeutics than was the case a few years ago. The use of vaccines in whooping cough, however, is still highly recommended by many who have had occasion to use this therapy in private and institutional practice. Recently Luttinger[1] reported favorably on the use of this vaccine after an experience with a whooping cough clinic in New York City. However, Van Sholle, Blum and Smith[2] concluded from the same clinical material that "more observations and more critical observations with controls for comparison must be made before the case can be made out for the curative and prophylactic value of pertussis vaccine." Their results were quite the opposite to those of Luttinger. Shaw[3] used pertussis vaccines as a prophylactic on 164 children exposed in four different epidemics, and found that only 7 per cent. of the number developed the disease.

It will thus be seen that there is a striking lack of uniformity in the conclusions. The present study is in a measure the continuation of one which was reported from this institution in 1914 by Hess.[4] In the course of an epidemic during that year various vaccines were used, including an autogenous strain, for the purpose of both curative and prophylactic therapy. This investigation was carried out on a large number of children, and the conclusion was drawn that although the vaccine did not seem to be of value in curing the disease or lessening its severity, it did seem to have some prophylactic value. Twenty of the children vaccinated, however, developed pertussis in spite of the prophylactic inoculations. In 1917, when this disease again visited our

* Submitted for publication April 15, 1918.

*From the Home for Hebrew Infants, New York City.

1. Luttinger, P.: Pertussis Vaccine, Jour. Am. Med. Assn., 1917, **68,** 1461.

2. Van Scholle, A., Blum and Smith: The Therapeutic Value of Pertussis Vaccine in Whooping Cough. Jour. Am. Med. Assn., 1917, **68,** 1451.

3. Shaw, H. L. K.: The Treatment of Whooping Cough. New York State Jour. Med., 1918, **18,** 18.

4. Hess, A. F.: Use of a Series of Vaccines in the Prophylaxis and Treatment of an Epidemic of Pertussis. Jour. Am. Med. Assn., 1914, **63,** 1007.

institution, it was decided once more to attempt to determine the value of this therapy in pertussis. The cases may be divided into five groups:

1. Early prophylactic treatment.
2. Later prophylactic treatment.
3. Unvaccinated.
4. Curative vaccination.
5. Patients who had received prophylactic treatment in 1915 as well as curative or prophylactic treatment in this epidemic.

The vaccine used was that prepared by the municipal laboratory of New York City, and the dosage given was that which they recommend, and was in excess of that which had been used in the previous epidemic.

TABLE 1.—Data of Twelve Patients Who Developed Pertussis in Spite of Prophylactic Vaccination Two to Three Weeks Prior to Coming in Contact with Active Cases *

Name	Date of Vaccination	Date of Exposure	Date of Onset	Severity	Per Cent.	Duration (Weeks) of			Aver. Duration of Paroxysm, Weeks
						Cough	Whoop	Vomiting	
M. G.	7/6, 7/8, 7/10	7/22	9/29	Mild	..	4	1	0	
H. S.	7/6, 7/8, 7/10	7/22	8/24	Mild	..	6	6	0	
S. W.	6/28, 7/5, 7/11	7/22	8/15	Mild	..	8	6	0	
P. W	7/8, 7/10, 7/12	7/22	8/22	Mild	..	5	3	2	
M. H.	6/28, 7/5, 7/11	7/22	8/14	Mild	..	4	4	4	
S. B.	7/8, 7/10, 7/12	7/22	7/31	Mild	..	7	5	0	
A. B.	7/8, 7/10, 7/12	7/22	8/ 9	Mild	59	3	2	2	4
S. S.	6/28, 7/5, 7/11	7/22	8/31	Moderate	..	6	6	4	
I. J.	6/28, 7/5, 7/11	7/22	8/10	Moderate	16	6	5	2	5½
B. W.	6/28, 7/5, 7/11	7/22	7/28	Severe	..	10	8	3	
M. K.	7/6, 7/8, 7/10	7/22	8/ 5	Severe	..	10	10	9	
A. G.	7/6, 7/8, 7/10	7/22	8/14	Severe	2.5	12	9	6	9

* Twenty-nine patients (70 per cent.) thus treated did not develop pertussis.

1. *Early Prophylaxis.*—In most prophylactic vaccination researches the question always has arisen as to whether the patients had not possibly become infected, and were not in the incubation period of the disease before the vaccine was resorted to. This is especially true in relation to pertussis, which has a long incubation period and indefinite onset. For example, if a child showed symptoms of the disease some ten days after vaccination, it could not be stated with certainty that the virus had not entered the body before the vaccines were resorted to. We were particularly fortunate in this epidemic in being able to observe a group of patients to which this criticism was not applicable. It so

happened that forty-one children in the isolation house were given a series of vaccinations three weeks or more before they were transferred to the main building where the epidemic broke out. If we are

TABLE 2.—DATA OF 114 PATIENTS WHO DEVELOPED PERTUSSIS IN SPITE OF PROPHYLACTIC VACCINATION *

Length of Time Pertussis Followed Prophylactic Vaccination	Number of Cases	Severity	Average Duration (Weeks) of			Remarks
			Cough	Whoop	Vomiting	
2 weeks	27	Mild..... 9	4	2½	3 days	1 child had pertussis in 1914 also; received prophylactic vaccination in 1914
		Moderate. 4	8	6	3	1 child had prophylactic vaccination in 1915
		Severe..... 10	16	15	5	4 children received prophylactic vaccination in 1915
3 weeks	21	Mild..... 9	5	3½	4 days	1 child was exposed to whooping cough in 1915 and 2 had prophylactic vaccination in 1915
		Moderate. 5	9	6	3½	1 child received prophylactic vaccination in 1915
		Severe..... 7	11	7	6	
4 weeks	29	Mild..... 20	5	4	4 days	1 child received prophylactic vaccination in 1915
		Moderate. 5	7½	6	2	
		Severe..... 4	11½	10	4	3 children received prophylactic vaccination in 1915
5 to 7 weeks	21	Mild..... 12	5⅔	3⅔	2 days	
		Moderate 5	8	6	3	1 child received prophylactic vaccination in 1915
		Severe..... 4	11	11	3	2 children had a recrudescence after 5th week
8 to 12 weeks	16	Mild..... 9	3½	1	0	Very mild group of cases
		Moderate. 3	8	8	3 days	
		Severe..... 4	12	11	3½	1 case; recrudescence after 7th week

* One hundred and sixty-six children (59 per cent.) did not develop pertussis.

to regard this period of time as sufficient for the child to produce its immune bodies, which would seem correct, judging from the analogy in animals, we can feel certain that these children must have been protected to the greatest possible extent. Table 1 illustrates the

results on this group of cases. It will be seen that twelve developed pertussis, and that twenty-nine, or about 70 per cent., did not develop this disease. It will also be noted that although most of these cases were mild, there were three which were exceptionally severe, lasting on an average about nine weeks. We shall postpone drawing any conclusions from these results until we consider the next group of children who were also given prophylactic treatment.

2. *Later Prophylactic Treatment.* — This group consisted of 220 children who were in the building where the epidemic took place and were unavoidably exposed to infection, as there were active cases in each ward. They received prophylactic treatment in the same manner as the former group. Of this number, 114, or 41 per cent., contracted

TABLE 3.—DATA OF NINE UNVACCINATED CHILDREN WHO DEVELOPED PERTUSSIS *

Name	Severity	Duration (Weeks) of			Remarks
		Cough	Whoop	Vomiting	
G. I.	Mild	8	3	0	
H. F.	Mild	7	4	0	
I. S.	Mild	4	2	0	
E. E.	Moderate	9	7	0	
H. C.	Severe	16	12	7	Epistaxis; received prophylactic vaccination in 1915
H. C.	Severe	11	9	5	Received prophylactic vaccination in 1915
D. K.	Severe	11	6	3	Epistaxis
H. B.	Severe	18	16	8	
I. G.	Severe	15	14	7	Hematemesis

* Nine others did not develop this disease.

pertussis from two to twelve weeks after vaccination. About half of these cases were mild, especially those that came down from two to three months after vaccination, which may be due to the fact that the epidemic was already on the decline. The average duration of the paroxysmal stage will be noted to have been forty-two days (Table 2). It is of special interest that in this group, eleven children had prophylactic treatment during the 1915 epidemic of whooping cough and that nevertheless, in spite of this double protective therapy, they came down with the disease.

In view of the rarity of recurrence in pertussis we wish to report that one of our patients had whooping cough in 1914; this attack was very mild, lasting only twelve days.

3. *Unvaccinated.*—Of the eighteen children who did not receive any treatment, nine contracted pertussis. About one third followed a mild course; however, the average duration of paroxysmal coughing was about eight weeks.

TABLE 4.—DATA OF TWENTY-EIGHT PATIENTS WHO RECEIVED THREE CURATIVE INJECTIONS

Name	When Treatment Began	Severity	Duration (Weeks) of			Remarks
			Cough	Whoop	Vomiting	
R. A.	6 days before onset	Mild	5	4	0	
L. B.	3 days before onset	Mild	6	5	0	Recrudescence after the 4th week
L. F.	8 days before onset	Mild	6	3	2	
S. S.	1st week after onset	Mild	3	2	0	
H. A.	1st week after onset	Mild	3	2	0	Received prophylactic vaccination in 1915
W. S.	1st week after onset	Mild	5	1	0	
G. C.	1st week after onset	Mild	5	1	0	
A. S.	2d week after onset	Mild	6	5	0	
H. S.	2d week after onset	Mild	6	4	3	
Ch. S.	3d week after onset	Mild	7	2	0	
H. S.	3d week after onset	Mild, 39%	7	1	0	
T. F.	6 days before onset	Moderate	7	4	1	
H. K.	8 days before onset	Moderate	9	6	0	
S. P.	1st week after onset	Moderate	8	3	2	
A. R.	1st week after onset	Moderate, 14%	7	5	2	Received prophylactic vaccination in 1915
I. W.	8 days after onset	Severe	16	13	5	Recrudescence after the 8th week
M. G.	8 days after onset	Severe	7	4	4	Hematemesis
G. C.	6 days before onset	Severe	21	21	7	Developed pneumonia and empyema; died
N. M.	4 days before onset	Severe	10	5	4	
A. K.	4 days before onset	Severe	9	5	1	
H. V.	8 days before onset	Severe	11	8	6	Received 4 injections
M. P.	1st week after onset	Severe	10	10	0	
S. K.	1st week after onset	Severe	15	13	12	Received prophylactic vaccination in 1915
H. S.	1st week after onset	Severe	11	8	4	Received 4 injections
M. L.	2d week after onset	Severe	8	6	6	
I. R.	2d week after onset	Severe	11	8	4	
M. G.	3d week after onset	Severe	24	24	20	Recrudescence after the 8th week
S. S.	8 days before onset	Severe, 47%	14	12	5	

4. *Curative vaccination.*—Twenty-eight children received the curative treatment by three injections of the vaccine. Some of the very severe cases received even four injections, the last two consisting of two billion bacteria.

TABLE 5.—Data of Twenty-Three Patients Who Had Received Prophylactic Vaccination in 1915 as Well as Curative or Prophylactic Treatment During This Epidemic

Character of Vaccination	Number of Cases	Severity	When Treatment Began	Average Duration (Weeks) of			Remarks
				Cough	Whoop	Vomiting	
Curative	8	Mild, 4	First week	4	2	3 days	
		Severe, 4	First week	12	10	6	Two cases epistaxis
Prophylactic	15	Mild, 5	Two cases 2 wks. and three cases 4 wks before onset	5½	3	1½	One case had whooping cough in 1914
		Moderate, 2	2 wks. after onset	7½	6	3½	
		Severe, 8	Five cases 2 wks. and three cases 4 wks before onset	12	11	5½	

TABLE 6.—Summary of Tables 1, 2, 3, 4 and 5

Group	No. of Cases	When Treatment Was Given	Number of Cases Contracting W. C.	Average Duration (Weeks) of			Per Cent. Not Developing W. C.	Severity of Disease, per Cent.
				Cough	Whoop	Vomiting		
Early prophylactic	41	6-12 wks. before onset	12	6	5	2	70	Mild, 59 Moderate, 16 Severe, 25
Later prophylactic	280	2-12 wks. before onset	114	8	6	2	59	Mild, 52 Moderate, 22 Severe, 26
Double prophylactic (1915 and 1917)	60	15 cases 2-4 wks. before onset, 8 cases 2-4 wks. after onset	23	7	6	3	61	Mild, 39 Moderate, 8 Severe, 53
Curative*	28	From 1 wk. before to 1-2 wks. after onset	..	9	5	3	..	Mild, 39 Moderate, 14 Severe, 47
Nonvaccinated	18	.....	9	9	8	3	50	Mild, 33 Moderate, 11 Severe, 56

* These cases received three injections.

Naturally, we were able to begin treatment early; this is one of the advantages of a study of this kind, carried out in an institution with a physician in constant attendance. Indeed, we have included in this group of "curative cases" fifteen children who received injections three days to a week before manifesting symptoms of the disease. It will thus be seen that in our analysis we have given the therapy the benefit of every doubt. Table 4 gives the results in a conclusive manner. Without doubt the vaccine accomplished little, for 60 per cent. of the cases must be classed as severe.

In conclusion we would call attention to a group comprising twenty-three children who had received prophylactic treatment in 1915 as well as curative or prophylactic treatment during this epidemic, but who, notwithstanding this fact, contracted pertussis. We found that the duration and severity in these cases did not differ, to all appearances, from the other cases.

CONCLUSIONS

As a result of the use of vaccines in this epidemic of pertussis we are led to about the same conclusions which Hess reached in 1914 following a similar therapeutic test. It would seem almost certain that pertussis vaccine, given even in large dosage, not only has no curative effect, but does not tend to lessen the severity of the disease. The experiences of these two epidemics can be interpreted only in this way.

As regards the prophylactic value of pertussis vaccine, the case is different. In both the former epidemic and in this one the percentage of vaccinated children who developed the disease was considerably less than of those who were not vaccinated. If we draw conclusions from our own results we must therefore attribute to the vaccine some prophylactic potency.

We wish to emphasize the fact that in this study it was possible, for the first time, to vaccinate children some weeks before they came in contact with cases of pertussis, and that therefore there was no chance of their having been in the incubation stage at the time prophylactic therapy was instituted.

I desire to thank Drs. A. F. Hess and Sidney V. Haas for permission to publish this study, and Dr. Julius Blum, pathologist of this institution, for his assistance.

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FURTHER REPORT ON THE USE OF PERTUSSIS VACCINE CONTROLLED BY THE COMPLEMENT FIXATION TEST*

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In a previous communication[1] I gave a preliminary report on the prophylactic use of pertussis vaccine controlled by the complement fixation test. In this paper it was shown that, by means of the complement fixation test, it was possible to demonstrate specific antibody formation after the prophylactic injection of pertussis vaccine. The conclusions arrived at were as follows:

> Our observations in seventeen cases would, theoretically, justify the prophylactic vaccination against pertussis. In none of the cases treated with the smaller doses could any antibodies be demonstrated, whereas, large doses, such as recommended by the New York City Health Department, showed antibodies in 44 per cent. of cases. The freshly prepared vaccines were, apparently, more effective than the stock vaccines, as 60 per cent. of the patients treated gave positive fixation reaction. From this it may be concluded that it is possible to immunize children against pertussis if sufficiently large doses of freshly prepared pertussis vaccine be given.

Since that time it has been possible to continue and extend this work at the Minnesota State Hospital for Crippled Children.[2]

In the first series of four cases, a three months old vaccine, prepared by the New York City Department of Health, was used. Three doses of one-half billion, one billion and two billion bacteria were given on alternate days. The complement fixation test before the administration of the vaccine and two weeks after, was negative in all four cases. In the second series, of ten cases, a vaccine was employed, freshly prepared from three strains of Bordet-Gengou bacilli, in the same dosage of one-half billion, one billion and two billion bacteria, on alternate days. (Our original cultures were obtained through the courtesy of the New York City Health Department.) The complement fixation test, before the administration of the vaccine, was negative in all cases; two weeks after the last injection the test was markedly positive in nine cases and questionably positive in the tenth. A third series of four cases was given a com-

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* Read in the Section on Diseases of Children of the American Medical Association at its sixty-ninth annual session, Chicago, June 12, 1918.
* From the Department of Pediatrics and the Department of Bacteriology, University of Minnesota.

1. Huenekens, E. J.: Am. Jour. Dis. Child., 1917, **14**, 283.
2. I wish to take this opportunity to thank Drs. Gillette and Christison for extending to me the privileges of the hospital.

mercial vaccine—from the label on the bottle, presumably two months old. This was given in three doses, one billion, one and one-half billion and two billion; all were negative before, two remained negative one week afterward, one was doubtfully and one definitely positive. Little significance was attached to a doubtfully positive reaction. A fourth series of nine cases gave a negative complement fixation test. A freshly prepared vaccine was then injected, every third day, in three doses of one billion, one and one-half billion and two billion. A complement fixation test performed one week after the last injection gave a markedly positive reaction in all nine cases. Of these last nine cases, three had slight temperature reaction after the second dose; none after the other doses. The fever was ephemeral, lasting but a few hours, in two cases reaching as high as 101 F.; in the third case 100 F. To summarize the last four series, four cases that were given three months old vaccine showed no evidence of antibody formation; four cases, given two months old commercial vaccine, gave a distinctively positive reaction in only one case, or 25 per cent. Of the nineteen given freshly prepared vaccine, eighteen gave a markedly positive reaction and one a questionably positive reaction, or 94 per cent. In the last nine cases, in which a larger dosage was used, one, one and one-half and two billion, there were 100 per cent. positive reactions and these could be elicited within one week after the last injection.

Studies were made to determine how long the positive complement fixation test persisted. Of the cases giving a positive reaction after the prophylactic injection of vaccine, it was possible to test thirteen after the lapse of three months. Three were found to be still positive; the other ten had become negative. With the lapse of six months, all reactions were negative, including the three who had still been positive at three months.

What is the significance of this? Does it mean that all immunity has been lost? Immunologists are agreed that, in such cases, while the antibodies may have disappeared from the blood, a considerable immunity still remains; for the patient, having once gone through the process of antibody formation, is able to repeat the process more readily and more quickly in subsequent infections. This is illustrated in typhoid fever, where the positive Widal reaction after a period of time disappears, but the immunity to typhoid persists.

It finally remained to be determined what constitutes a fresh vaccine. At what age does it begin to lose its efficacy? For this purpose three vaccines were prepared and were given, one when two weeks old, another when three weeks old and the third at four weeks. Twelve cases were employed, four for each vaccine, in the dosage of one, one and one-half and two billion. The four patients given four weeks old vaccine gave positive reaction in two cases, or 50 per cent.,

the cases given three weeks old vaccine gave 25 per cent. positive reactions, while the two weeks old gave 75 per cent. positive reactions. It follows, therefore, that a two weeks old vaccine has begun to deteriorate.

An interesting point in this connection is that the freshly prepared vaccine is very cloudy, while the older vaccines are clear or nearly so. Dr. Larson, of the Bacteriology Department of the University of Minnesota (to whom I am greatly indebted for assistance and helpful suggestions), has made the interesting observation, in his work with other vaccines, that autolysis sets in shortly after the preparation of a vaccine, that the process is usually complete in about three weeks, and that, as a result of this autolysis, the vaccine changes from cloudiness to a clear solution. He believes that an autolyzed vaccine has entirely lost its antigenic properties.

Another advantage of fresh vaccine is that no preservative is employed.

Pick[3] has shown that egg albumin which has been treated by some disinfectant, such as iodin, phenol or nitric acid, is materially altered, in that immune serum produced against such treated antigen does not react with normal antigen, that is, untreated egg albumin.

DISCUSSION

The fact that antibody formation takes place within a week after the third injection of vaccine would indicate that fresh pertussis vaccine may be used, not only as a prophylactic, but also in the treatment of the disease if the patient is seen in the early stages. This would mean that, owing to the difficulty of diagnosing pertussis in the early catarrhal stage, the vaccine should be employed on mere suspicion during an epidemic, especially where there is a history of known exposure. It may be argued that the difficulty in obtaining fresh pertussis vaccine is so great as seriously to interfere with its usefulness. But the difference in activity of freshly prepared and old pertussis vaccine is so marked, as proved conclusively by this work, that the attempt to put fresh pertussis vaccine on a practical basis should be made. Commercial laboratories, by constantly keeping on hand cultures of several strains of pertussis bacilli, should be able to supply the vaccine on short notice and at a moderate cost.

SUMMARY AND CONCLUSIONS

Pertussis vaccine from two to three months old, employed in very large doses, one billion and over, immunizes in only 12½ per cent. of cases.

3. Kolle-Wassermann: Handbuch, Vol. 1.

Two to four weeks old vaccine confers immunity in from 25 to 75 per cent. of cases.

Freshly prepared vaccine, employed in the same dosage, shows evidence of antibody formation in 94 per cent. of cases. When used in still larger doses, one, one and one-half and two billion, 100 per cent. positive reactions are obtained.

The antibodies are demonstrable within one week after the last injection.

The following conclusions, therefore, seem warranted:

Pertussis vaccine should be employed only when freshly prepared and without preservative. By fresh vaccine is meant a vaccine less than one week old.

The most effective dosage is one billion, one and one-half billion and two billion, given on alternate days, for three doses.

It is most effective as a prophylactic, but should be of great value in the early catarrhal stage of pertussis.

In doubtful cases of pertussis the vaccine should be administered before an exact diagnosis can be made, especially during an epidemic or where there is a history of previous exposure.

Physicians and Surgeons Building.

A PROTECTIVE THERAPY FOR VARICELLA, AND A CONSIDERATION OF ITS PATHOGENESIS *

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As is well known, chickenpox is one of the very mildest of the infectious diseases to which children are subject. It possesses, however, considerable medical interest, as one of the group of diseases of unknown origin, and furthermore, because of its remarkable communicability. In the latter particular it is rivalled only by measles. In the Home for Hebrew Infants it has been our experience that in the course of an epidemic about three quarters of the younger children develop varicella, and about one half of those above 2 years of age. It spreads rapidly through the institution, progressing from ward to ward in an uncontrollable manner, frequently necessitating quarantine for a period of many months. Among children in private homes it possesses a serious pedagogic aspect, often disrupting the school sessions for long periods because of its widespread prevalence and long incubation period, which causes the infection to drag along throughout the entire winter term. Therefore, when Kling,[1] in 1913, reported that he was able to immunize children against this mild but exceedingly disturbing infectious disease by means of a single vaccination, we welcomed the announcement and decided to make use of it at the earliest opportunity. Kling's method consisted merely of applying the contents of the vesicles to the abraded surface of the skin, after the manner in which a von Pirquet tuberculin reaction is carried out. Two years later a small epidemic of chickenpox made its appearance in our institution and Kling's method was put into practice. The result may be summarized by the statement that it afforded a certain degree of immunity, but that it was by no means satisfactory. This, we believe, has been the experience of others who have used this procedure. It seemed to point the way, however, to better methods. It was evident, from its partial success, that the virus was contained in the vesicles, and it seemed probable that its failure was due to a faulty and uncertain introduction of the virus.

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* Read in abstract, May 6, 1918, before the American Society for Clinical Investigation, and presented before the American Pediatric Society, Lenox, Mass., May 29, 1918.

1. Kling, C.: Berl. klin. Wchnschr., 1913, **50**, 2083.

During the past year varicella has been widespread throughout New York City, and made its appearance in our admitting pavilions. An opportunity was therefore afforded us again to attempt immunization. To this end we made use of the contents of the vesicles, but instead of applying this fluid to the surface of the skin, we injected it intravenously. The technic was as follows:

> In each instance only vesicles, and not pustules, were made use of; the surfaces were very gently washed with sterile salt solution and the contents allowed to ascend into capillary tubes. As much as possible of the clear fluid was obtained and was immediately mixed with sterile normal salt solution. This diluted virus was diluted still further with salt solution before it was injected. The dosage was entirely empirical, ¾ inch, as measured in the capillary tube, was used in each instance.[2]

In all, thirty-eight children, about 3 or 4 years of age, were vaccinated intravenously after this method. None of the children developed any local or general signs, or any eruption suggestive of varicella. They were all, in the course of the epidemic, unavoidably in contact with one or more cases of chickenpox, but in spite of this proximity only one developed the disease, this one thirty-six days after the date of inoculation.

It is evident, therefore, that by means of these intravenous vaccinations almost absolute immunity was brought about, and no symptoms of the disease. This result, paradoxical as it may at first appear, may be interpreted as follows: It would seem that most viruses are able to bring about their specific diseases only when they are introduced in their natural paths, or rather, that if they are introduced by other routes, an excessive amount of the virus is required to produce a specific reaction. Varicella, a disease of the lymphatic system, does not enter the body by means of the blood stream, and its virus has not acquired the property of invading the human organism by this path. It was this line of reasoning which led us to undertake this mode of therapy.

Camus[3] found, in his experiments on smallpox, that it required a very much larger amount of variola virus to produce this disease in rabbits when the intravenous, instead of the cutaneous, method was employed, and recently Noguchi[4] noted a similar phenomenon in experimenting with his testicular virus. The latter reports that in order to produce an eruption one thousand times more virus had to be introduced by way of the blood stream than applied on the skin.

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2. All children in the institution who have a large spleen, bilateral epitrochlear glands, or give a family history of insanity, are subjected to the Wassermann test, so that all danger of syphilis was guarded against.

3. Camus, L.: Compt. rend. Soc. de biol., 1913, **75,** 344.

4. Noguchi, H.: Jour. Exper. Med., 1918, **27,** 425.

It is interesting to note in this connection that Noguchi showed that the lymph glands harbored the virus; this may likewise hold true for varicella.

The vesicular lymph was given also in other ways, as will be seen by consulting Table 1. It will be noted that in a number of cases it was introduced intravenously after having been inactivated by exposure to a temperature of 56 C. for three quarters of an hour. In sixteen instances the unheated lymph was injected intracutaneously; in ten, subcutaneously, and in a few cases was placed on the broken skin, on the mucous membrane of the nose, on the tonsils and buccal mucous membranes, and on the mucous membranes of the nose and mouth.

It seemed as if these methods might afford a simpler technic, and one which would avoid the somewhat difficult intravenous puncture. It will be seen from the table, however, that the number of these cases which came into intimate contact with the varicella were too few to allow us to judge of the success of these attempts at vaccination. Two facts, nevertheless, stand out in sharp relief: first, that no instance of primary varicella, even of the mildest type, resulted from these attempts at immunization and, second, that only the intravenous method was shown to afford adequate protection. The latter conclusion is inevitable in view of the fact that chickenpox developed about two months later in one of the three cases in which the lymph was placed on the broken skin (von Pirquet), and in two of the three cases in which it was applied to the nostrils. These few tests suffice to show the inefficacy of these simpler methods.

About three years ago Herman[5] made an attempt to immunize infants under 6 months by applying to the nostrils nasal mucus from children having measles. He carried this out in forty cases and believed that he had brought about immunity in a certain number of instances. In the light of this report, and its simplicity, it seemed worth while to make a similar attempt on a small number of cases in relation to varicella. In view of the fact that the vesicular lymph, which is known to contain the varicella virus, did not induce the slightest disorder when applied this way, it was evident that no disturbance was to be apprehended from this procedure. In three instances the nasal secretion of varicella patients was applied to the nostrils; in three others the tonsillar secretion to the tonsils, and in six, the tonsillar and pharyngeal secretions were transferred to the nose, the pharynx, and the tonsils. In none of these twelve cases was there any reaction whatever, either local or systemic. In two, secondary varicella developed in the course of the epidemic, from six to eight weeks later — one, where the nasal secretion was employed, and another where the ton-

5. Herman, C.: Arch. Pediat., 1915, **32**, 503.

sillar secretion was made use of. It is therefore evident that this method cannot be relied on to bring about protection. This is all the more striking in view of the fact that of these twelve cases only six came in intimate contact with varicella, so that we must consider that two of the six failed to develop immunity to the disease.

Incidentally, these tests furnish interesting information as to the portal of entry of the virus of varicella. The fact that the lymph from the vesicles, when applied to the broken skin or to the mucous membranes, led to no infection must cause us to consider this investigation from quite another standpoint. How are we to explain this lack of infectivity of the contents of the vesicles, which are generally regarded as the source of infection, and are used as the criterion in prescribing the duration of quarantine? There seems to be but one logical inter-

SUMMARY OF PROTECTIVE IMMUNIZATION

Mode of Introduction of Lymph	Number of Cases*	Number Subsequently in Contact with Chickenpox	Number of Contacts Developing Chickenpox	Remarks
Intravenous	38	38	1	Chickenpox appeared in this case 41 days following prophylactic therapy
Intravenous (inactivated)	9	1	0	
Intracutaneous	16	5	1	No local reaction
Subcutaneous	10	0	—	
Skin (v. Pirquet)	3	3	1	Chickenpox 62 days after immunization
Nostrils	3	3	2	Chickenpox 44 and 62 days after immunization
Tonsils and mouth	3	3	0	
Tonsils, nose and mouth	4	0	—	

* There was no instance of signs or symptoms of varicella occasioned by the immunization.

pretation of these results, namely, that the lymph was in no instance applied to its natural portal of invasion. The only other possibility—that the virus is not present in the vesicle—is apparently refuted by our experience that immunity was brought about by injections of this fluid. What is, then, Nature's path of invasion? These vaccinations afford strong testimony — of a negative character, it is true — for an answer to this question. In view of our results, and the highly infectious nature of this disease, we are led to the tentative conclusion that the virus is air borne, and that its portal of entry frequently is the respiratory tract.

CONCLUSIONS

It is possible to bring about immunity to varicella by means of an intravenous injection of the contents of the vesicles. In thirty-eight instances in which this was carried out it failed to protect in only one

case. Vaccinations of this kind induce neither local nor systemic reaction. The acquisition of immunity likewise indicates that the specific virus is contained in the vesicles. A simpler method of therapy, the application of the lymph to the broken skin or mucous membranes, failed to bring about satisfactory immunity, although it also occasioned no disorder.

These investigations have a secondary bearing as to the natural portal of entry of the varicella virus into the body. As we can exclude the skin and the mucous membranes in this connection, it would seem most probable that the virus enters by way of the respiratory tract, and that contagion comes about through the air. This mode of infection would account for the almost unexampled communicability of this disease.

16 West Eighty-Sixth Street.

ENERGY METABOLISM OF AN AMAUROTIC FAMILY IDIOT *

FRITZ B. TALBOT, M.D.
BOSTON

The following case of amaurotic family idiocy was obtained from the Children's Hospital through the kindness of Dr. John Lovett Morse, and studied under the direction of Dr. F. G. Benedict at the Nutrition Laboratory of the Carnegie Institution of Washington, Boston, Mass.

HISTORY OF CASE

History.—The child, B. D., girl, aged 2 years and 4 months, was admitted to the hospital Nov. 22, 1916. The father and mother, brother and sister were living and well, and were of normal mental and physical development. There was a normal family history.

The patient was born of a normal pregnancy and labor, and was breast fed for one year, during most of which time she had a severe facial eczema. At 3 to 4 months she first noticed her hands, but never made any effort to use them except to play with a rattle, when it was placed in them. If she dropped the rattle, she was unable to find it, nor could she pick it up if her hands came in contact with it by accident. She never played with anything else, and had never been able to hold up her head or sit up.

Dec. 24, 1915, she had a convulsion during which the extremities jerked for an hour or more, the eyes were rolled up, and she perspired and drooled. In February, 1916, she entered the Infants' Hospital and Dr. George H. Derby found on examination of the eye grounds, "secondary atrophy of the optic nerve heads, and cherry-red spots in the macular regions with edema about them." She entered the Children's Hospital because she was mentally backward, could not see, and was only able to take liquid food. She took no notice of her surroundings, and lay quietly except when startled by a noise, which could cause a temporary clonic convulsion of all the extremities. Except during these periods of spasm, she lay absolutely still, without any voluntary movement.

Physical Examination.—This showed an underdeveloped, poorly-nourished child, lying quietly in bed, drooling constantly and taking no notice of the surroundings. The extremities were cold and the feet slightly blue. The head was large in proportion to the body. Both pupils reacted to light, but the right was slightly larger than the left. They were regular in outline. The physical examination otherwise revealed nothing abnormal except that the extremities were spastic and markedly atrophied. There were no signs of voluntary motion. The von Pirquet test was negative. The white count was 9,800. The urine was acid, cloudy, straw colored and contained the slightest possible trace of albumin. The sediment contained many pus cells. Lumbar puncture, 8 c.c., clear fluid under normal pressure. Cell count 7, of which one was a leukocyte and six were epithelial cells. The Wassermann reaction was

* Submitted for publication June 4, 1918.
* Read at the meeting of the American Pediatric Society, Lenox, Mass., May, 1918.
* From the Nutrition Laboratory of the Carnegie Institution of Washington, Boston.

negative. From December 5 to 12, the week preceding the time that the metabolism was observed, the child's temperature was subnormal, the lowest being 95.5 F. At times during this period the pulse registered 69. This was lower than the careful pulse records taken during the metabolism periods. She never cried and lay absolutely quiet in bed except when disturbed by a sudden, loud noise or by being touched. External stimuli of this sort caused clonic convulsive movements. During this period she simply existed in bed, taking her food as it was given to her. She died Dec. 26, 1916, probably of inanition as a result of pyelitis and amaurotic family idiocy.

Necropsy.—Postmortem examination by Dr. S. B. Marlow showed a few facts of importance when taken in connection with the metabolism. The body was 75 cm. long and showed extreme emaciation. The skin was everywhere loose, and even on incision showed no subcutaneous fat. The muscles were atrophied and showed very little rigor mortis; they were pale and thin in appearance. There was no fat in the mesentery or the retroperitoneum. In fact, the absence of fat was so conspicuous that special emphasis was laid on it in the report of the pathologist. The brain nowhere filled the cranium and was from 0.5 to 1 cm. distant from the bony wall of the skull. The dura over it was loose and collapsed, giving the impression that it had been previously distended with fluid. The meninges about the spinal cord were edematous and distended. The eye when removed showed at the macula a deep colored spot about 1.5 cm. in diameter, surrounded by a gray ring 2 mm. wide. The rest of the examination showed nothing of importance to record here.

The child had, therefore, amaurotic family idiocy and pyelitis. She was extremely thin and emaciated, and moved in bed only when disturbed by sound or touch. The amount of muscular activity during the day was so slight that it was almost negligible, except during the colonic convulsions. There was no storehouse of fat on which to draw for energy when desired, as is found in the new-born infant. Although most of the remaining body tissue was muscle, bone and organs, the muscles were thin and atrophic, and could not, therefore, be said to represent normal muscle. Although clinically the actions of this infant were similar to those of the child without any cerebral hemispheres, previously reported by me,[1] physically the two infants were quite different. In this case there was an almost complete absence of fat, while in the other, the body was composed almost entirely of fat. Table 1 gives the energy metabolism of B. D. The length of the periods of observation of this baby and the babies subsequently reported was, in all instances, thirty minutes.

Although the weight of these normal infants is quite close to, and in most instances almost identical with, that of B. D., their length is much shorter and, therefore, they are much fatter. However, they give an idea of what B. D.'s metabolism should have been if the body had been developed normally in relation to the weight. The basal metabolism of B. D., compared to that of three normal infants of the same weight, is very low (approximately 30 per cent. lower than the normal for the weight).

1. Talbot, F. B.: Arch. Pediat., 1915, **32,** 452.

TABLE 1.—BASAL ENERGY METABOLISM OF B. D.*

Date	Body Weight and Surface	Height, Cm.	Heat Produced per 24 Hours				Average Pulse Rate	Relative Activity
			Total Cals.	Per Kilogram, Cals.	Per Sq. Meter			
					Lissauer, Cals.	DuBois Linear, Cals.		
12/11/16	6.41 kg. $10.3\sqrt[3]{wt_2}$ = 0.355 sq. m. Du Bois Linear = 0.408 sq. m.	76	283†	..	...	...	83	Active
			246	38	693	603	83	Quiet
			250	39	704	613‡	86	Quiet
			250	39	704	613	91	Quiet

* One ounce of milk was taken four hours before observations were commenced.
† Preliminary period not used in calculation.
‡ Average respiratory quotient, 0.82. Temperature, rectal, 97 F. beginning of periods: 96.8 F. at end of periods.

TABLE 2.—COMPARISON OF BASAL METABOLISM OF B. D. WITH THAT OF NORMAL INFANTS OF APPROXIMATELY THE SAME WEIGHT

Name	Age, Mos.	Body Weight Without Clothing, Kg.	Height, Cm.	Heat Produced per 24 Hours				Periods Averaged	Pulse Rate
				Total Cals.	Per Kilogram, Cals.	Per Sq. Meter			
						Lissauer, Cals.	DuBois Linear, Cals.		
1. B. D.	28	6.41	76	249	39	700	610	3	87
2. M. C.* (normal infant)...	4	6.17	63	333	54	967	...	7	103
3. R. A.* (normal infant)...	7	6.42	65	358	56	1,002	...	3	118
4. N. D.* (normal infant)...	7	6.79	67	381	56	1,032	...	5	100

* Benedict and Talbot: AM. JOUR. DIS. CHILD., 1914, **8**,, 1.

TABLE 3.—COMPARISON OF BASAL METABOLISM OF B. D. WITH THAT OF NORMAL INFANTS OF THE SAME AGE

Name	Age, Mos.	Body Weight Without Clothing, Kg.	Height, Cm.	Heat Produced per 24 Hours				Periods Averaged	Pulse Rate
				Total Cals.	Per Kilogram, Cals.	Per Sq. Meter			
						Lissauer, Cals.	DuBois Linear, Cals.		
1. B. D.	28	6.41	76	249	39	700	610	3	87
2. M. R.*.....	25	10.96	79	617	56	1,214	1,135	3	104
3. Gr. Mc.L.*.....	26¼	12.24	88	605	49	1,107	1,028	3	96
	29½	12.82	91	602	49	1,101	1,025	4	112

* Not previously reported.

The metabolism of these normal infants gives an idea of what the metabolism of B. D. would have been had she developed normally for her age. Her total metabolism is less than half that of three average normal infants, and her metabolism per unit of body weight or body surface were both decidedly low.

The metabolism of this amaurotic family idiot is, therefore, very low both when compared to that of normal infants of either the same weight or normal infants of the same age. Her metabolism is comparable to that of J.J. M. who had no cerebral hemispheres,[1] and, therefore, moved only when stimulated to do so by touch. This child moved both when touched and when disturbed by noise. The body was run at such a low economic level that very little food was necessary for life.[1]

TABLE 4.—COMPARISON OF METABOLISM OF PATHOLOGIC CHILDREN

Name	Age, Mos.	Body Weight Without Clothing, Kg.	Height, Cm.	Heat Produced per 24 Hours				Pulse Rate
				Total Cals.	Per Kilogram, Cals.	Per Sq. Meter		
						Lissauer, Cals.	DuBois Linear, Cals.	
1. B. D.	28	6.41	76	249	39	700	610	87
2. J. J. M.	8	8.43	73.5	230	28	560	...	73
3. Cretin, C. G.[2]	44	11.83	85	464	39	867	...	95

The interpretation of the metabolism of B. D. is extremely difficult, as we have a picture of great emaciation, in which a large proportion of the body tissues are muscle with almost no fat. The pulse rate, which, at the time of the observation, was relatively high or normal for the age,[3] was low at times in the hospital. Under these conditions a high metabolism rather than a low metabolism might have been expected, as has been recorded in the findings of Publication 201 of the Carnegie Institution of Washington. As a matter of fact, the metabolism was very low. The rectal temperature of 97 F. during the period of observation was not an extremely subnormal temperature, but it

2. Talbot, F. B.: AM. JOUR. DIS. CHILD., 1916, **12**, 145.

3. In designating the pulse rate of B. D.—83 to 91, as shown in Table 1—as high, or relatively high, it must be remembered that it is not logical to say the pulse rate in a given individual is abnormally high. It has been often pointed out in the Nutrition Laboratory of the Carnegie Institution of Washington, that it is not permissible to argue that a high pulse rate in any given individual absolutely implies a high metabolism. What is more important is the deviation from the normal pulse rate of that individual.

is not impossible that this may be an indication of lowered vital activity, although it is quite unreconcilable with the relatively high pulse rate.

In conclusion, this child with amaurotic family idiocy presents a very unusual and complicating situation, in which the metabolism may have been modified either by the subnormal temperature, by emaciation, by the plane on which the baby was living, or by the disease, and does not present any simple explanation. It is hoped that other records of the metabolism of amaurotic family idiots will clear up the doubtful point presented in this picture.

311 Beacon Street.

A COMBINED TEMPERATURE, WEIGHT, FOOD, SYMPTOM, ETC., RECORD CHART FOR PEDIATRIC WORK*

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CLEVELAND

The putting down on one sheet in a graphic and easily legible form the most important factors concerned in determining the picture and the course of a disease, as well as the therapy instituted to control it, is obviously a great advantage over the old and still quite universally practiced method of using different sheets for different data. The newer method not only saves much time, but enables one to correlate at a glance many of the observations into a picture of the whole. The idea is not original, as it was seen and used by one of us in its developed form in 1910 at the Kaiserin Augusta Victoria Haus in Charlottenburg.

The chart of this institution was ruled for thirty-one days, and was a most elaborate affair, providing not only for recording the temperature, pulse, respiration, weight, food, stools, symptoms, treatment, calories, etc., but also for various data regarding the parents, the confinement, the diagnosis and condition on admission and discharge, etc. In consequence it was awkwardly large, measuring approximately 15¼ by 20½ inches, and in addition the proportion of the length to the width of that part of the chart recording the weight made the angle of the weight curve too acute, about 23 degrees for a daily gain of 30 gm., which, according to Heubner, as quoted by Langstein and Meyer,[1] should be 39° 45′ for an average daily gain of 26.6 gm. during the first three postnatal months. These dimensions also made impossible much of a rise or fall in the weight chart, except as a result of a very large gain or loss, 20 gm. gain or loss causing a movement of the curve for a vertical distance of but 7/48 of an inch. Finally, the temperature, pulse and respiration charts could hardly be ruled accurately with an economic use of time, as no vertical rulings existed in the chart, except the lines separating one day from the other. On the whole, however, this chart was an improvement, and it was with the idea of applying its good points to our local hospital records that the present chart was devised.

As it was our idea to have all of the pediatric wards in which local medical school teaching was being carried out use the same chart-

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* From the Babies' Dispensary and Hospital, City Hospital and Lakeside Hospital, Cleveland.

* Read by title at the meeting of the American Pediatric Society, Lenox, Mass., May, 1918.

1. Langstein and Meyer: Säuglingsernährung und Säuglingsstoffwechsel, J. F. Bergmann, 1910, p. 41.

ing and recording scheme, in order to aid in making the whole department uniform, we were bound closely to the present forms and sizes of the records of Lakeside Hospital and City Hospital, the Babies' Dispensary having adopted for its Out-Door Ward no rigid form or size of chart. Consequently, the largest electrotype that we could use was one measuring 8⅝ inches in width and 10⅝ inches in length, which at Lakeside Hospital had to be printed on paper measuring 8⅝ by 11 inches, while at City Hospital and at the Out-Door Ward of the Babies' Dispensary and Hospital the more spacious sheet of 9½ by 12 inches could be used. Our present ideas regarding a more ideal size will be indicated further on.

In the chart here presented the following innovations or changes have been made:

1. The space for the recording of the weight and food has been given dimensions which make possible the formation of a weight angle of about 35 degrees with a daily gain in weight of about 30 gm.

2. As a result of this change there has been made available more space for the recording of "Treatment" and "Symptoms." In this connection it may be said that the symptoms are not described in detail, but simply given in an appellative manner. Whenever a detailed description is desirable, this must be noted in the regular history sheet.

3. The space for the individual day has been divided by three vertical lines into four spaces. This arrangement makes it possible for the nurse quickly and easily to find the correct space for the notation of the temperature degree and pulse and respiration rates, according to the hour of the day. By dividing the daily space into four parts, it is possible to make an accurate notation of the pulse, respiration, etc., every twelve hours, every six hours, or every three hours. While the space for the last is small, yet experience has shown that it is ample, owing to the ever-present oscillation in the different curves.

4. The second of the third vertical lines mentioned under 3 has again been divided into ten equal parts, so that it really is an equally divided dotted line. This has been done to give the recording nurse an accurate and rapid guide for the notation of the temperature degree, the weight figure and the pulse and respiration rates. The last two are not frequently recorded, however, so the division is usable mainly in the registering of the temperature curve and the weight curve. Although the weight curve occasionally goes down into the food space, the dotted line has not been extended down beyond the space for the registering of the temperature curve, in order sharply to differentiate the one large space from the other.

5. The space for the recording of stools has been divided into the two periods, a. m. and p. m., and it has also been increased in size, in order that the individual stools might be described if desired.

6. The electrotype has been printed in a light coffee-brown or a light gray, in order that the colors used in recording the temperature, pulse, weight, and respiration might stand out more clearly. Von Pirquet has also used a different color than black for his charts, but the one he chose, a brownish-yellow, is difficult to see with artificial light.

At the Kaiserin Augusta Victoria Haus, a color scheme was used for the charting of the different food mixtures. In one department of that institution different colored and gummed paper slips were properly pasted into the food space, while in the other department the different colors were put on the food chart by using crayons. The former scheme is possibly somewhat neater, but also more complicated, as the various food modifications require a definite color of their own. With the crayon method fewer colors are necessary, because two colors can be used together in a corresponding proportion to designate the corresponding quantity of the foods as they exist in the food mixture, and if a nurse is at all careful and sketches the colors with a light hand, a very neat and permanent record can be made with simple and inexpensive crayons that can be purchased in the market.

On the pediatric service at Lakeside Hospital the chart and the following definite color and figure scheme have been used exclusively for fifteen months consecutively, so that a practical test really has been obtained.[2] Only a few minor changes in recording the feedings have been made.

Food Chart.—The colors named have been used to designate the following foods:

Whole milk, ultramarine blue
Skimmed milk, prussian blue
Whey, cobalt blue
S. M. A., violet
Plain buttermilk, chrome green, light
Koeppe's buttermilk, olive green
Casein milk, green, medium
Water, magenta
Oatmeal water, English vermilion
Barley water, madder lake
Potato water, Indian red
Cornstarch water, venetian red
Keller's soup, burnt umber
Keller's soup, modified, gold ochre
Tea, yellow
Breast milk, orange
"Refused," black

The total amount of food taken is sketched into the proper space of the food chart. If the amount taken does not correspond to the amount ordered, the difference is sketched in black above the amount taken, so that the space filled in with black designates the amount refused, and the total space occupied by both black and the food color represents the total amount ordered. As a result of this innovation of

2. Much credit and appreciation in this connection are due Miss L. O. Essery and Miss M. Francis, head nurses of Wards A and K, Lakeside Hospital.

charting the amount refused in the manner described, one obtains a beautiful picture of the appetite of the child.

If it is desirable to note the amount of water taken by the child besides the food, this is either noted in one of the free spaces below the "Additional Nourishment" space or (and this is the plan which we have adopted) it is charted in the daily "Food" space, in the color corresponding to water, just as the food is charted in the same space, except that the amount of water taken is charted from the top down and the food from the bottom up.

The actual mixtures in the daily food are indicated in direct proportion in the color scheme. So, if an infant is to have one-third milk and two thirds oatmeal water, one-third of the daily food space up to the figure representing the amount taken is colored with ultramarine blue, and two-thirds with English vermilion.

The percentage and kind of carbohydrate or salts (sodium chlorid, sodium bicarbonate) added to plain water or to the different food mixtures are indicated by writing with a hard black crayon, in the upper part of the food color column, the following letters and figures:

L = Lactose
S = sucrose
D = dextrose
Lv = levulose
DM = dextri-maltose
M = Mellin's food
MS = malt soup

SC = sodium chlorid
SB = sodium bicarbonate
1 = 1 per cent. of total mixture
1½ = 1.5 per cent. of total mixture
2 = 2 per cent. of total mixture
2½ = 2.5 per cent. of total mixture
3 = 3 per cent. of total mixture, etc.

So the appearance of "3 S" just below the top of a 600 c.c. color column, representing one-third milk and two-thirds oatmeal water, would indicate that 18 gm. of sucrose had been added to the total to make a 3 per cent. addition of sucrose to the 600 c.c. mixture of one-third milk and two-thirds oatmeal water.

The number of feedings in twenty-four hours is noted just above the bottom of the color column for a given food mixture by writing in black with a crayon, Roman figures corresponding to the number of feedings ordered. In the foregoing example a "VI" in black at the bottom of the 600 c.c. column — one-third milk and two-thirds oatmeal water—would mean that the child was to receive 6×100 c.c. in twenty-four hours.

If a change in the food should be ordered, and so during one day a child receive two kinds of foods, the first mixture given is sketched at the bottom of the column and the second directly above it.

Illustrative examples of most of the points just made can be found in the accompanying charts.

Additional Nourishment Notes. — The additional nourishment column is used for the recording of vegetables, cereals, zwieback, etc.

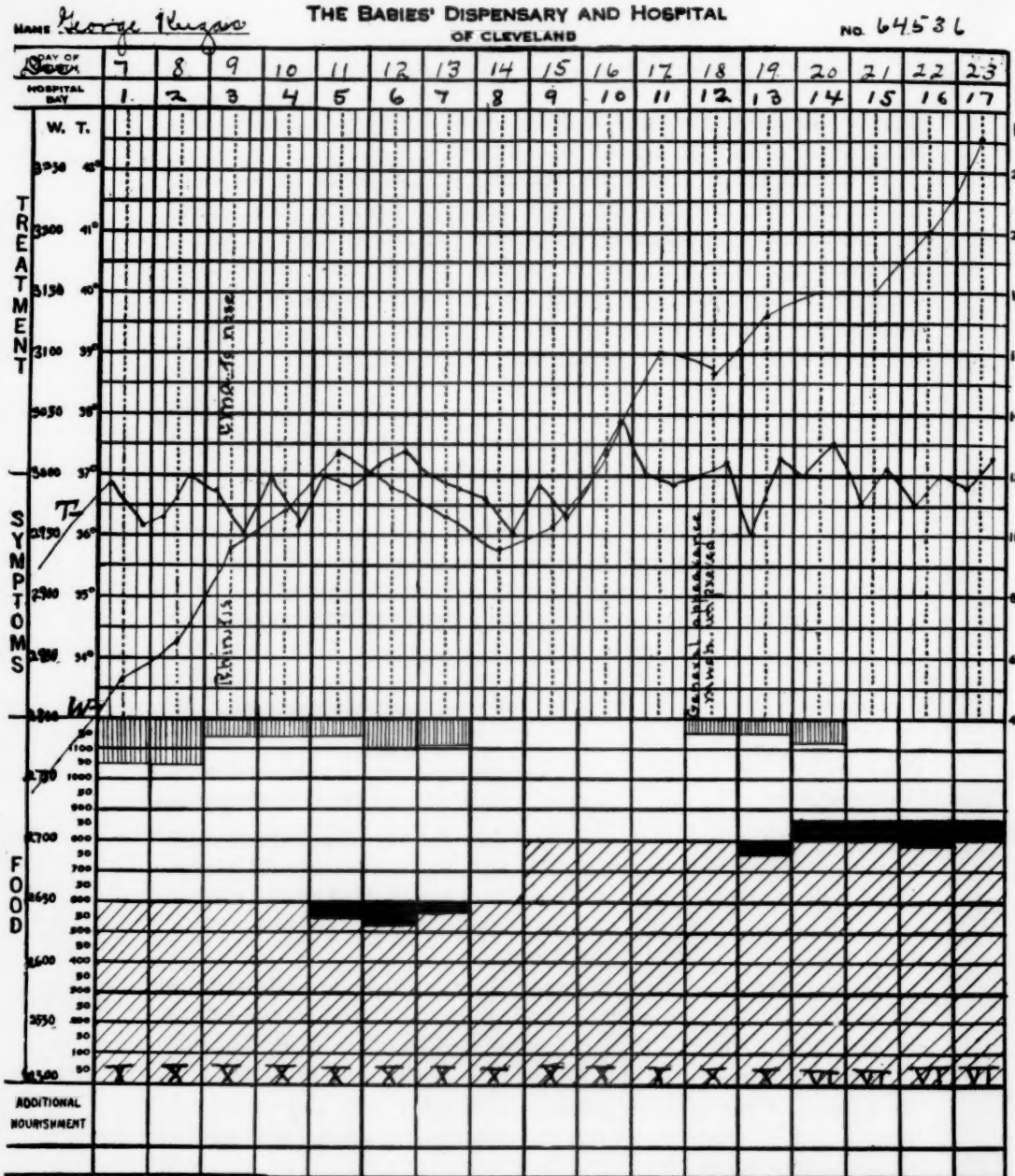

Fig. 1.—Example of authors' chart in use. The black line marked "T" is the temperature curve; the line marked "W" in the original chart is in red ink and is the weight curve. The portion shaded with diagonal lines represents Synthetic Milk Adapted and in the original chart in practical use is colored violet. The portion shaded with vertical lines represents water and in the chart in practical use is colored magenta. A complete description of the color scheme and other data recorded on the charts will be found in the text. About two-thirds actual size.

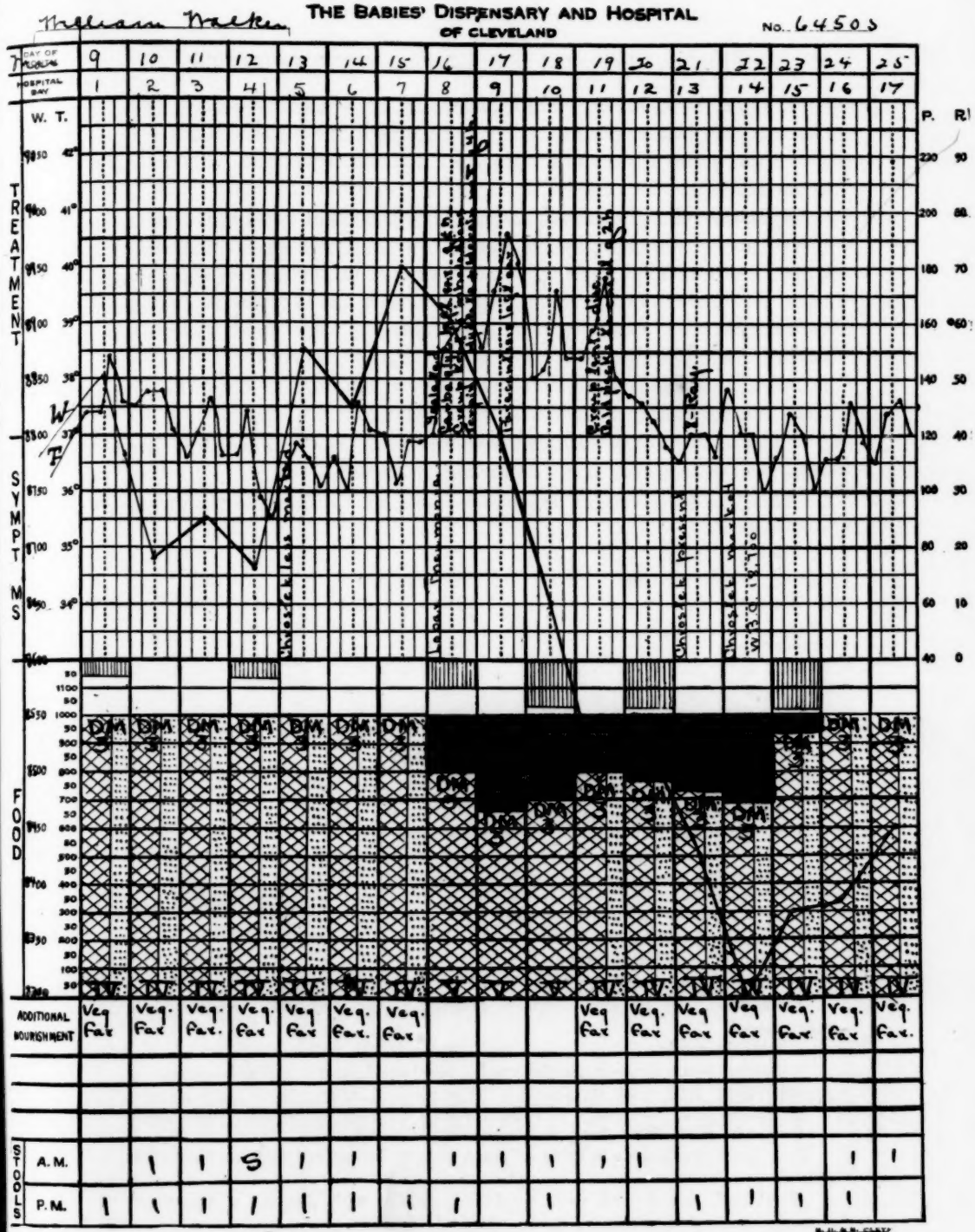

Fig. 2.—Another example of authors' chart. T he lines T and W indicate temperature and weight curves, respectively. The lattice hatching represents whole milk and in the chart in practical use this area is colored ultramarine blue; the dotted columns represent oatmeal water and in the chart as used in the hospital the area is colored English vermilion; the portion shaded by vertical lines represents water and in the chart in use is colored magenta. About two-thirds actual size.

Weight, Temperature, Pulse and Respiration Chart.—The weight curve is sketched in red ink (W); the temperature curve in black ink (T); the pulse curve in purple ink; and the respiration curve in green ink.

Symptoms and Treatment Notes.—The treatment notes are written in red ink on the chart by the nurse, and the symptoms in black ink by the intern or clinical clerk. Two colors are used clearly to separate these contiguous notes, and the black has been used for the recording of the symptoms simply because it is desired to make these notations during the ward visit or immediately after, and, under these circumstances, black ink is at all times available, in the form of the ordinary black ink fountain pen, for every intern and clinical clerk.

Stool Chart.—The color scheme has also been utilized, together with the sign scheme, in the recording of stools.

The following crayon colors are used to indicate the following stool colors:

Crayon	*Stool*
Chrome yellow, medium	Lemon yellow
Gold ochre	Yellow-brown
Orange	Orange-carrot yellow
Madder lake	Beet red
Chrome green, light	Yellow-green
Chrome green, dark	Green
Olive green	Gray-slate
Burnt umber	Brown—Keller's, older children, hemorrhage
Black	Bismuth—old blood

| = formed soft stool.

\ = semi-solid, soft stool of salve-like consistency.

\ = a thin stool whose consistency is between a watery stool and a semi-solid, salve-like stool. In many children this is not abnormal.

— = watery stool and abnormal, as far as consistency is concerned.

~~~ = squirting, watery stool seen only in marked diarrhea.

′ = mucus, slight in amount.

″ = mucus, medium in amount.

‴ = mucus, marked in amount.

c = choppy, stringy stool, usually greenish-yellow and with mucus = dyspeptic stool.

C = casein curds.

s = soft, putty-like, or partly sandy, semi-solid, gray, yellowish-gray, or greenish-gray fatty soap stool.

S = hard, dry, pale gray, very light yellow or green-gray fatty soap stool.

F = soft, thin, shiny fatty stool, usually yellowish.

b = blood streaked on outside of stool, usually bright red and mechanical in origin.

B = blood, mixed well with stool and usually with pus, of a brown-red tomato-sauce color, seen mainly in enteritis follicularis.

H = blood, bright red or dark brown or black, when very large in amount. and due to hemorrhage, as in intussusception, typhoid or hemorrhagic diseases.

P = pus, usually mixed with blood, in enteritis follicularis.
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Metric System.—It will be noticed that only the metric system has been used in this chart. This is in conformity with the plan which one of us inaugurated at the Babies' Dispensary during 1906, since which time all of the weight amounts, temperature degrees, and food amounts have been determined according to the metric system, not only for the physicians and nurses, but for the public as well, and it has been continued for added reasons: (1) in practically all scientific work of the various civilized countries the metric system is used, and (2) we believe that if it is more generally used in practical institutions like hospitals, dispensaries, etc., it will help toward its adoption by the public at large for their own daily personal use.

Pasting of Chart Sheets.—Even with the smallest sheet, 8⅝ by 11, it is possible, if so desired, to make one continuous chart out of the individual seventeen-day chart sheets by simply using a photographic trimming knife and library paste.

Ideal Chart Size.—Earlier in the article it was indicated that the form of the chart as presented today was determined by local conditions, and that ideally we should prefer a somewhat different form. From the experience which one of us has had at Lakeside Hospital during a period of fifteen months, this ideal electrotype size should at present measure 9^{23}⁄$_{24}$ inches wide by 13^{14}⁄$_{15}$ inches long. The increase in width would add three days to the chart, making a total of twenty days. The increase in length of the present chart is applied as follows:

1. The "Temperature" space is increased to 6¾ inches.
2. The "Food" space is increased to 4^{1}⁄$_{20}$ inches.

These alterations will change the angle of the weight curve for a daily gain of 25 gm. to 37° 21′, which would correspond with Heubner's figures of 39° 45′ for an average daily gain of 26.6 gm. This change also gives still more space in the "Symptom" and "Treatment" columns for the respective notations.

3. The "Additional Nourishment" space is increased to ^{35}⁄$_{48}$ of an inch.
4. The blank spaces for extra notes under the "Additional Nourishment" space are increased in number from three to four.

This new form could be printed on paper measuring 10 by 14⅜ inches, corresponding with 8⅝ by 11 in the present chart, or better on a larger sheet measuring 10⅞ by 15⅜ inches, corresponding with 9½ by 12 in the present chart.

IS THE AMOUNT OF CALCIUM USUALLY GIVEN IN DILUTIONS OF COW'S MILK INJURIOUS TO INFANTS?*

A REPLY TO THE ARTICLE ON "CALCIUM IN ITS RELATION TO THE ABSORPTION OF FATTY ACIDS," BY BOSWORTH, BOWDITCH AND GIBLIN, IN THE AMERICAN JOURNAL OF DISEASES OF CHILDREN, JUNE, 1918

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The claim is made by Bosworth, Bowditch and Giblin that by the use of a special "reconstructed" or "decalcified" milk, infants who are artificially fed will have a no greater excretion of fat in the feces than those fed at the breast. The position is taken that this special milk provides an improved form of feeding over simple cow's milk dilutions, because on the latter, children suffer a serious loss of fat through the excretion of soap stools; also that there follows from such feeding excessive constipation, leading frequently to a general upset, termed by the authors a "blowup."

We have had no opportunity to study Bosworth's decalcified milk and its effects; but we desire to present some conclusions drawn from results obtained in this laboratory which may perhaps allay the fears of calcium injury from the use of simple dilutions of cow's milk in infant feeding.

There are three questions suggested by this article which we desire to discuss:

1. Is there a serious loss of fat (otherwise than through diarrhea) when the usual simple dilutions of cow's milk are fed?

Of a group of thirty-two children from 2 to 15 months of age whom we have studied, eight received over 25 gm. of fat daily, the highest intake being 47 gm. None of the entire group had any tendency to diarrhea. Twenty-nine had a fat retention of 89 per cent. or more of the intake, eighteen having over 90, and ten over 95 per cent. Only two of the whole group retained less than 80 per cent. of the intake, these retaining 78.9 and 78.2, respectively.

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* Submitted for publication June 12, 1918.

* From the Laboratories of the Babies' Hospital and the Rockefeller Institute for Medical Research, New York.

Table 3 in the article by Bosworth, Bowditch and Giblin, when analyzed, shows much lower percentages of fat retained than the foregoing values. Of the twenty-three cases in their table, only ten show a fat retention above 84 per cent., only two over 90 per cent. and none over 95 per cent., while in eleven the fat retention is less than 80 per cent. The difference between their results and ours is brought out in Table 1.

TABLE 1.—Comparison of Figures for Fat Retention

	Bosworth et al.	Babies' Hospital Laboratory
Per cent. of total number with over 95 per cent. retention	0.0	31.3
Over 90 per cent	8.7	56.3
Over 84 per cent	43.5	90.6
Under 80 per cent	47.8	6.2

We have not found such low percentages of fat retained as their figures show, except in cases of diarrhea, and occasionally in infants fed on protein milk. In the latter the intake of fat and the absolute retention are usually higher than with other milk preparations.*

The extremely low fat retentions shown in Table 3 of the article by Bosworth, Bowditch and Giblin raises the question whether in all their cases the excretion reported fairly corresponds to twenty-four hours' intake, or is excessively large because of a diminished excretion on the preceding day or two. This possibility occurs to us because of the peculiarity of the calcium excretion given in their Table 1. Computing from the formula used — fat 2 per cent., sugar 6 per cent., protein 1.6 per cent. — and the daily intake of 795 c.c., the total calcium intake could not have been more than 0.70 gm. of calcium oxid (CaO). The total calcium excretion reported is 1.697 gm., an excess over the intake of nearly 1.0 gm. of CaO. This we consider to be most improbable, being greater than we have ever found, even in the most severe cases of rickets. Such excretion, however, might be accounted for, if the stools had been small, or if there had been none on the two preceding days. On this supposition the intake for three days would be approximately 2.1 gm., making, with the excretion reported, a positive balance of 0.4 gm., or about 0.13 gm. per day, which is a small retention. The daily fat excretion would then become about 1.84 gm., giving a retention of 14.06 gm., or 88.5 per cent. of the intake, a not unusually low retention for perfectly normal infants.

Bosworth and Bowditch claim that the high calcium content of the intake causes a serious loss of fat as soaps in the stools of bottle-fed infants. Accordingly, we present below some figures which may tend

* The protein milk employed in the Babies' Hospital is made from whole milk, not from skimmed milk.

to reassure those who are likely to be alarmed over the "abnormality" of the large quantities of calcium soaps in the stools. In the group of thirty-two children just referred to, nineteen were receiving calcium to the extent of over a gram of CaO daily. Of these, only six had as much as 2 gm. of fat as soaps in the daily stools. All but one were utilizing over 85 per cent. of the ingested fat, while four absorbed more than 95 per cent. Table 2 shows the per cent. of fat retained and the amount of fat excreted as soaps by the children in this group who had the highest calcium intakes.

TABLE 2.—FAT RETENTION AND FAT EXCRETED WITH HIGH CALCIUM INTAKE

Gm. CaO Intake	Per Cent. Fat Retained	Gm. Fat Excreted as Soap
1.80	95.8	0.78
1.66	89.4	1.68
1.50	93.2	1.12
1.47	87.7	0.79
1.41	87.1	1.76
1.39	95.5	0.99

A study of Table 2 shows that the maximum output, in the feces, of calcium bound as soaps was about 0.18 gm., since the combining weight of the higher fatty acids found in the stools is about ten times that of calcium oxid. Thus, it can be seen that the calcium which goes to form soaps is only a small part of the calcium intake.

Bosworth and Bowditch claim, however, that it is the degree of solubility of the calcium of the food which influences the formation of soaps. Using Bosworth's estimate of the "condition of calcium in cow's milk," which he gives in Table 6, the soluble calcium is seen to form 29.2 per cent. of the total calcium. In our entire series of thirty-two cases previously mentioned, the calcium which could possibly be held as soaps invariably falls below 25 per cent. of the intake. In the six with very high intake of calcium, the amount of calcium which could be held as soaps ranges from 7.0 to 12.5 per cent. of the intake, running well below half of Bosworth's estimate of the soluble calcium of the food. This proves conclusively that not all the soluble calcium is eliminated in the feces in the form of soaps. The inference that a high calcium intake causes a serious loss of fat does not seem to be warranted.

In a group of forty-six breast-fed infants, whose stools have been studied in this laboratory, twenty-five had over 40 per cent. of the fat excretion in the form of soaps. Thus, the presence of a considerable proportion of calcium soaps in the stools cannot be called an "abnormality," if breast-fed infants are to be taken as a standard. In one case, in which an exact record of the intake of breast milk was obtainable, the following results were found. With an intake of 41.9 gm. of

fat, the total fat excretion was 2.26 gm., of which 63.8 per cent. was soap. The fat retention was 94.6 per cent. of the intake. The calcium intake was 0.355 gm. This child was at the time doing extremely well and has continued to do so. In this baby with a small calcium intake, practically the same results were found as with many bottle-fed infants with two or three times the calcium intake. This child had for its age (about 1 month) an unusually large fat intake.

It is conceded that breast-fed infants retain a high *percentage* of their fat intake and in many cases retain a large actual *amount* of fat. This may possibly be due to the biologic factors of the natural food rather than to any advantage in its chemical composition. Bosworth and Bowditch maintain that the soap excretion is dependent on the proportion of soluble calcium in the food, and on this ground explain the lower soap fat excretion when the food is breast milk. According to their Table 6, however, cow's milk, after being diluted with an equal volume of water, contains but little more soluble calcium than does breast milk, that is, 0.0225 gm. of calcium in 100 c.c., in comparison with 0.021 in breast milk.

2. Is there danger of constipation with serious consequences in infants fed on simple dilutions of cow's milk?

Among the stools from the thirty-two children before mentioned, there was only one which from its appearance could be called constipated. The child was 7½ months old and was doing well with an intake of 47.0 gm. of fat daily. The retention was 93.7 per cent. of the intake, the excretion of soap fat 2.3 gm. daily. The child has continued to gain and has done well without interruption up to the present. Two other children, 14 weeks and 8 months of age, respectively, were reported to be constipated. Though the stools of the latter were induced by a daily enema, the feces of both these children were soft and pasty and the daily amount small. They had, respectively, a retention of 96 and 97 per cent. of the intake, with daily soap fat excretion of 0.5 and 0.3 gm. This sort of constipation depends rather on the muscular tone of the bowel and on training than on the chemical composition of the stool. A tendency to constipation in infants receiving simple cow's milk dilutions is generally controlled without great difficulty. On the other hand, the desirability of formed or semi-formed soap stools in contrast to the ever dreaded tendency to diarrhea in bottle-fed infants, particularly in evidence in hospital patients, can hardly be overestimated. It is probably for this reason that protein milk with its high calcium and fat content plays so important a part in the control of diarrhea. Necessarily the formed stool has a large proportion of its fat in the form of calcium soaps, but, as has been pre-

viously emphasized, the total loss of fat in this way is very seldom, if ever, of serious consequence.

3. May there not be a danger in too low a calcium intake?

Unless the harm caused by a fairly high calcium intake can be quite definitely demonstrated, it would seem safer to allow an excess of calcium in the intake rather than to run any risk of providing less calcium than is needed for the normal growth of the bones. A number of cases of so-called intestinal infantilism have come under our observation. The most significant fact in the history of these cases is the extremely low intake of calcium in their previous feeding. The large calcium requirement of children with a tendency to rickets hardly needs mentioning in this connection. The calcium in breast milk, though smaller in quantity, may be more available than that of cow's milk; however, it is well known that many cases of rickets and tetany occur in children fed too long exclusively on breast milk.

In conclusion, we believe it is yet to be demonstrated that infants fed on simple dilutions of cow's milk do not retain an adequate amount of fat, when the stools are formed or semiformed and soapy; nor do we think that a high calcium intake necessarily causes a large fat loss in the feces; while a great reduction of the calcium in the food of infants may be attended with considerable risk.

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